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(54) Title: SALTS AND SOLVATES OF GLUCAGON ANTAGONISTS

(57) Abstract: The invention provides salts and solvated of glucagon antagonists.

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SALTS AND SOLVATES OF GLUCAGON ANTAGONISTS

FIELD OF INVENTION

The present invention relates to salts and solvates of glucagon antagonists.

BACKGROUND OF THE INVENTION

The invention relates to glucagon antagonist as previously disclosed in published patent applications WO 99/01423, WO 00/39088, WO00/42026, WO 00/69810, WO 02/00612, WO 02/40444, WO 02/40445 and WO 02/40446, WO03/048109, WO03/51357, WO03/53938, WO03/97619 (Novo Nordisk A/S) disclose glucagon antagonists and other glucagon antagonists.

The compounds areuseful as glucagon antagonist and in the treatment of hyperglycemia, Type 1 diabetes, Type 2 diabetes, disorders of the lipid metabolism, such as dyslipidemia, and obesity as well as in treatment of other diseases.

For pharmaceutical and commercial use it is important to have an active compound with properties such as for example good stability, non-hygroscopicity, high melting point, good bioavailability, good handling properties, high degree of crystallinity and a reproducible crystalline form.

The present invention thus provides suitable salts and solvates of the compounds of the invention. For example, the salts and solvates of the invention provide stable compounds under storage and accelerated storage conditions as a model for long term stability.

SUMMARY OF THE INVENTION

The invention provides a composition comprising a salt or a solvate of a glucagon antagonist.

In an aspect of the invention a composition is provided comprising a salt of a glucagon antagonist and a pharmaceutically acceptable base

In an aspect of the invention the glucagon antagonists are described in the published applications WO 99/01423, WO 00/39088, WO00/42026, WO 00/69810, WO 02/00612, WO 02/40444, WO 02/40445 and WO 02/40446, WO03/048109, WO03/51357, WO03/53938 and WO03/97619 and as described in this application below.

In an embodiment of the invention the basic counter ion are derived from ammonium or imidazole or the metal ions of lithium, sodium, potassium, magnesium, calcium, zinc, or the basic amino acids L-arginine, L-lysine, L-histidine, and L-ornithine; or alkylated ammonium derivatives such as di-ethylamine, tert-butylamine (erbumine), 1,2-ethylenediamine, N-(phenylmethyl)-benzeneethaneamine (benethamine) or N,N'-dibenzylethylenediamine (benzathine); or hydroxyalkylated ammonium derivatives trishydroxymethylaminomethane (tris, tromethamine), N-methyl-D-glucamine (meglumine), choline, monoethanolamine (2-aminoethanol, olamine), di-ethanolamine (2,2'-iminobis(ethanol)), tri-ethanolamine (2,2',2''-nitrilotris(ethanol), trolamine), 2-diethylaminoethanol.

In an aspect of the invention a composition is provided comprising a solvate of a glucagon antagonist.

In one aspect of the invention the solvate is formed from a class III solvent (ICH Guidelines Q3C; "Impurities: Guidelines for Residual Solvents", 1997).
In another aspect the solvate is formed from one of the solvents: ethanol, 2-propanol, 2-methyl-1-propanol, n-butanol, 2-butanol, 3-methyl-1-butanol, diethyl ether, *tert*-butyl-methylether, tetrahydrofuran, anisol, acetone, 2-butanon, methylacetate, ethylacetate, n-propylacetate and toluene.

The present invention also relates to a process for the preparation and pharmaceutical compositions containing the compounds.

The present invention provides compounds as novel materials, in particular in pharmaceutically acceptable form.

Within another aspect of the present invention there is provided a method of using the compounds according to the invention for the treatment and/or prevention of diabetes and/or obesity.

DETAILED DESCRIPTION OF THE INVENTION

The following is a detailed definition of the terms used to describe the compounds of the invention:

"Halogen" designates an atom selected from the group consisting of F, Cl, Br and I.

The term "C_{1-6}-alkyl" or "lower alkyl" as used herein represents a saturated, branched or straight hydrocarbon group having from 1 to 6 carbon atoms. Representative examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, n-pentyl, isopentyl, neopentyl, *tert*-pentyl, n-hexyl, isohexyl and the like.

The term "C_{2-6}-alkenyl" or "lower alkenyl" as used herein represents a branched or straight hydrocarbon group having from 2 to 6 carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, iso-propenyl, 1,3-butadienyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl and the like.

The term "C_{2-6}-alkynyl" or "lower alkynyl" as used herein represents a branched or straight hydrocarbon group having from 2 to 6 carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 2,4-hexadiynyl and the like.

The term "C_{1-6}-alkoxy" or "lower alkoxy" as used herein refers to the radical -O-C_{1-6}-alkyl, wherein C_{1-6}-alkyl is as defined above. Representative examples are methoxy, ethoxy, n-propoxy, isopropoxy, butoxy, *sec*-butoxy, *tert*-butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy and the like.

The term "C_{1-6}-alkanoyl" or "lower alkanoyl" as used herein denotes a group -C(O)H or -C(O)-C_{1-5}-alkyl. Representative examples are formyl, acetyl, propionyl, butyryl, valeryl, hexanoyl and the like.

The term "C_{3-8}-cycloalkyl" or "cycloalkyl" as used herein represents a saturated, carbocyclic group having from 3 to 8 carbon atoms. Representative examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

The term "C_{4-8}-cycloalkenyl" or "cycloalkenyl" as used herein represents a non-aromatic, carbocyclic group having from 4 to 8 carbon atoms containing one or two double bonds. Representative examples are 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 2-cycloheptenyl, 3-cycloheptenyl, 2-cyclooctenyl, 1,4-cyclooctadienyl and the like.

The term "heterocyclyl" as used herein represents a non-aromatic 3 to 10 membered ring containing one or more heteroatoms selected from nitrogen, oxygen and sulfur and optionally containing one or two double bonds. Representative examples are pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, aziridinyl, tetrahydrofuranyl and the like.

The term "aryl" as used herein is intended to include carbocyclic aromatic ring systems such as phenyl, biphenylyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, pentalenyl, azulenyl and the like. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl and the like.

The term "aroyl" as used herein denotes a group -C(O)-aryl, wherein aryl is as defined above.

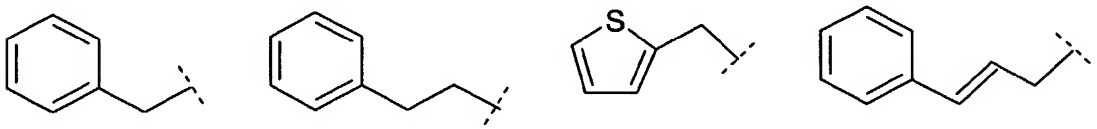
The term "aryloxy" as used herein denotes a group -O-aryl, wherein aryl is as defined above.

The term "arylene" as used herein is intended to include divalent carbocyclic aromatic ring systems such as phenylene, biphenylylene, naphthylene, anthracenylene, phenanthrenylene, fluorenylene, indenylene, pentalenylene, azulenylene and the like. Arylene is also intended to include the partially hydrogenated derivatives of the carbocyclic systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 1,2,3,4-tetrahydronaphthylene, 1,4-dihydronaphthylene and the like.

The term "heteroaryl" as used herein represents a heterocyclic aromatic ring system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur such as furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl,

1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5- triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzothiophenyl (thianaphthenyl), indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinolizinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl and the like. Heteroaryl is also intended to include the partially hydrogenated derivatives of the heterocyclic systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 2,3-dihydrobenzofuranyl, pyrrolinyl, pyrazolinyl, indolinyl, oxazolidinyl, oxazolinyl, oxazepinyl and the like.

"Aryl-C_{1-6}-alkyl", "heteroaryl-C_{1-6}-alkyl", "aryl-C_{2-6}-alkenyl" or "Aryl-lower alkyl", "heteroaryl-lower alkyl", "aryl-lower alkenyl" etc. mean C_{1-6}-alkyl or C_{2-6}-alkenyl as defined above, substituted by an aryl or heteroaryl as defined above, for example:



The term "optionally substituted" as used herein means that the groups in question are either unsubstituted or substituted with one or more of the substituents specified. When the groups in question are substituted with more than one substituent the substituents may be the same or different.

Certain of the above defined terms may occur more than once in the structural formulae, and upon such occurrence each term shall be defined independently of the other.

Crystalline salts with a well defined structure are preferred salts due to their stability.
The salts may form in different ratios between compound and salt. The ratio depend on the nature of the basic counter ion and of the compound. In an aspect of the invention salts are formed in a 1:1 ratio of compound to salt. In another aspect of the invention the salts are formed in a 2:1 ratio of compound to salt.

The composition as above wherein the pharmaceutically acceptable basic counter ion are derived from ammonium or imidazole or the metal ions of lithium, sodium, potassium,

magnesium, calcium, zinc, or the basic amino acids L-arginine, L-lysine, L-histidine, and L-ornithine; or alkylated ammonium derivatives such as di-ethylamine, tert-butylamine (erbumine), 1,2-ethylenediamine, N-(phenylmethyl)-benzeneethaneamine (benethamine) or N,N'-dibenzylethylenediamine (benzathine); or hydroxyalkylated ammonium derivatives trishydroxymethylaminomethane (tris, tromethamine), N-methyl-D-glucamine (meglumine), choline, monoethanolamine (2-aminoethanol, olamine), di-ethanolamine (2,2'-iminobis(ethanol)), tri-ethanolamine (2,2',2"-nitrilotris(ethanol), trolamine), 2-diethylaminoethanol.

In an embodiment of the invention the basic counter ions are selected from calcium, zinc, the amino acids L-arginine, L-lysine, L-histidine, and L-ornithine; N-methyl-D-glucamine (meglumine), choline, monoethanolamine (olamine), di-ethanolamine, tri-ethanolamine (trolamine), 2-diethylaminoethanol, tri-ethylamine, trishydroxymethylaminomethane (tris, tromethamine), 1,2-ethylenediamine or N,N'-dibenzylethylenediamine (benzathine).

In an embodiment of the invention the basic counter ion is selected from: L-lysine, L-arginine, L-histidine, tert-butylamine (erbumine), monoethanolamine (olamine), 1,2-ethylenediamine or N,N'-dibenzylethylenediamine (benzathine).

In an embodiment of the invention the basic counter ion is selected from : L-arginine, tert-butylamine (erbumine), or N,N'-dibenzylethylenediamine (benzathine).
In an embodiment of the invention the basic counter ion is N,N'-dibenzylethylenediamine (benzathine).

In an embodiment the ratio of compound to counter ion is 2:1 when the counter ion is N,N'-dibenzylethylenediamine (benzathine) or 1,2-ethylenediamine.

In an embodiment of the invention is provided solvates as a novel materials, in particular in pharmaceutically acceptable form. Consequently, only solvates which are physiologically acceptable in the amount administered to the subject in need of treatment are within the scope of the invention. Solvates between the parent compound and the following solvents are to be considered as being administrable to subjects: pentane, heptane, cumene, 1-propanol, dimethylsulfoxide, ethanol, ethyl formiate, formic acid, acetic acid, methyl acetate, ethyl acetate, n-propyl acetate, isopropylacetate, n-butylacetate, iso-butylacetate, methyl-isobutyl-ketone, 1-butanol, 2-butanol, 2-propanol, 2-methyl-1-propanol, 3-methyl-1-butanol, 1-

pentanol, diethyl ether, *tert*-butyl methyl ether, tetrahydrofuran, anisole, acetone, 2-butanone or toluene.

Stable solvates are arranged in stable conformations of solvent and parent compound which can be defined as a ratio of the parent compound to the solvate. The specific ratio between the two components is in the context of this invention not a limiting feature.

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming pharmacologically active substances. In general, such prodrugs will be functional derivatives of the compounds of the general formula (I), which are readily convertible *in vivo* into the required compound of the formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The invention also encompasses active metabolites of the present compounds.

The compounds according to the present invention act to antagonize the action of glucagon and are accordingly useful for the treatment and/or prevention of disorders and diseases in which such an antagonism is beneficial.

Accordingly, the present compounds may be applicable for the treatment and/or prevention of hyperglycemia, IGT (impaired glucose tolerance), insulin resistance syndromes, syndrome X, Type 1 diabetes, Type 2 diabetes, hyperlipidemia, dyslipidemia, hypertriglyceridemia, hyperlipoproteinemia, hypercholesterolemia, arteriosclerosis including atherosclerosis, glucagonomas, acute pancreatitis, cardiovascular diseases, hypertension, cardiac hypertrophy, gastrointestinal disorders, obesity, diabetes as a consequence of obesity, diabetic dyslipidemia, etc.

Accordingly, in a further aspect the invention relates to a compound according to the invention for use as a medicament.

The invention also relates to pharmaceutical compositions comprising, as an active ingredient, at least one compound according to the invention together with one or more pharmaceutically acceptable carriers or excipients.

The pharmaceutical composition is preferably in unit dosage form comprising from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg and especially preferred from about 0.5 mg to about 200 mg of the compound according to the invention.

Furthermore, the invention relates to the use of a compound according to the invention for the preparation of a pharmaceutical composition for the treatment and/or prevention of a disorder or disease, wherein a glucagon antagonistic action is beneficial.

The invention also relates to a method for the treatment and/or prevention of disorders or diseases, wherein a glucagon antagonistic action is beneficial the method comprising administering to a subject in need thereof an effective amount of a compound according to the invention.

In a preferred embodiment of the invention the present compounds are used for the preparation of a medicament for the treatment and/or prevention of any glucagon-mediated conditions and diseases.

In a preferred embodiment of the invention the present compounds are used for the preparation of a medicament for the treatment and/or prevention of hyperglycemia.

In yet a preferred embodiment of the invention the present compounds are used for the preparation of a medicament for lowering blood glucose in a mammal.

In another preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of IGT.

In still another preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of Type 2 diabetes.

In yet another preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from IGT to Type 2 diabetes.

In yet another preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of Type 1 diabetes. Such treatment and/or prevention is normally accompanied by insulin therapy.

In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of obesity.

In yet a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of disorders of the lipid metabolism, such as dyslipidemia.

In still a further embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of an appetite regulation or energy expenditure disorder.

In a further aspect of the invention the present compounds are combined with diet and/or exercise.

In yet a further aspect of the invention the present compounds are administered in combination with one or more further active substances in any suitable ratios. Such further active agents may be selected from antidiabetic agents, antihyperlipidemic agents, antiobesity agents, antihypertensive agents and agents for the treatment of complications resulting from or associated with diabetes.

Suitable antidiabetic agents comprise insulin, insulin analogues and derivatives such as those disclosed in EP 792 290 (Novo Nordisk A/S), eg $N^{\varepsilon B29}$-tetradecanoyl des (B30) human insulin, EP 214 826 and EP 705 275 (Novo Nordisk A/S), eg Asp^{B28} human insulin, US 5,504,188 (Eli Lilly), eg Lys^{B28} Pro^{B29} human insulin, EP 368 187 (Aventis), eg Lantus, which are all incorporated herein by reference, GLP-1 derivatives such as those disclosed in WO 98/08871 (Novo Nordisk A/S), which is incorporated herein by reference, as well as orally active hypoglycaemic agents.

The orally active hypoglycaemic agents preferably comprise imidazolines, sulphonylureas, biguanides, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon antagonists, GLP-1 agonists, agents acting on the ATP-dependent potassium channel of the β-cells eg potassium channel openers such as those disclosed in WO 97/26265, WO 99/03861 and WO 00/37474 (Novo Nordisk A/S) which are incorporated herein by reference, or nateglinide or potassium channel blockers such as BTS-67582, insulin sensitizers, DPP-IV (dipeptidyl peptidase-IV) inhibitors, PTPase inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, GSK-3 (glycogen synthase kinase-3) inhibitors, compounds modifying the lipid metabolism such as antihyperlipidemic agents and antilipidemic agents, compounds lowering food intake, PPAR (peroxisome proliferator-activated receptor) and RXR (retinoid X receptor) agonists such as ALRT-268, LG-1268 or LG-1069.

In one embodiment of the invention the present compounds are administered in combination with insulin or an insulin analogue or derivative, such as $N^{\varepsilon B29}$-tetradecanoyl des (B30) human insulin, Asp^{B28} human insulin, Lys^{B28} Pro^{B29} human insulin, Lantus, or a mix-preparation comprising one or more of these.

In a further embodiment of the invention the present compounds are administered in combination with a sulphonylurea eg tolbutamide, chlorpropamide, tolazamide, glibenclamide, glyburide, glipizide or glicazide.

In another embodiment of the invention the present compounds are administered in combination with a biguanide eg metformin.

In yet another embodiment of the invention the present compounds are administered in combination with a meglitinide eg repaglinide or nateglinide.

In still another embodiment of the invention the present compounds are administered in combination with a thiazolidinedione insulin sensitizer eg troglitazone, ciglitazone, pioglitazone, rosiglitazone, isaglitazone, darglitazone, englitazone, CS-011/CI-1037 or T174 or the compounds disclosed in WO 97/41097, WO 97/41119, WO 97/41120, WO 00/41121 and WO 98/45292 (Dr. Reddy's Research Foundation).

In still another embodiment of the invention the present compounds may be administered in combination with an insulin sensitizer such as GI 262570, YM-440, MCC-555, JTT-501, AR-H039242, KRP-297, GW-409544, CRE-16336, AR-H049020, LY510929, MBX-102, CLX-0940, GW-501516 or the compounds disclosed in WO 99/19313, WO 00/50414, WO 00/63191, WO 00/63192, WO 00/63193 (Dr. Reddy's Research Foundation) and WO 00/23425, WO 00/23415, WO 00/23451, WO 00/23445, WO 00/23417, WO 00/23416, WO 00/63153, WO 00/63196, WO 00/63209, WO 00/63190 and WO 00/63189 (Novo Nordisk A/S).

In a further embodiment of the invention the present compounds are administered in combination with an α-glucosidase inhibitor eg voglibose, emiglitate, miglitol or acarbose.

In another embodiment of the invention the present compounds are administered in combination with an agent acting on the ATP-dependent potassium channel of the β-cells eg tolbutamide, chlorpropamide, tolazamide, glibenclamide, glyburide, glipizide, glicazide, BTS-67582, repaglinide or nateglinide.

In still another embodiment of the invention the present compounds are administered in combination with an antihyperlipidemic agent or antilipidemic agent eg cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine.

In another aspect of the invention, the present compounds are administered in combination with more than one of the above-mentioned compounds eg in combination with metformin and a sulphonylurea such as glibenclamide or glyburide; a sulphonylurea and acarbose; metformin and a meglitinide such as repaglinide; acarbose and metformin; a sulfonylurea, metformin and troglitazone; a sulfonylurea, metformin and pioglitazone; a sulfonylurea, metformin and an insulin sensitizer such as disclosed in WO 00/63189 or WO 97/41097; a meglitinide such as repaglinide, metformin and troglitazone; a meglitinide such as repaglinide, metformin and pioglitazone; a meglitinide such as repaglinide, metformin and an insulin sensitizer such as disclosed in WO 00/63189 or WO 97/41097; insulin and a sulfonylurea; insulin and a meglitinide such as repaglinide; insulin and metformin; insulin, metformin and a meglitinide such as repaglinide; insulin, metformin and a sulfonylurea; insulin and troglitazone; insulin and pioglitazone; insulin and an insulin sensitizer such as such as disclosed in

WO 00/63189 or WO 97/41097; insulin and lovastatin; an insulin analogue or derivative, metformin and a meglitinide such as repaglinide; an insulin analogue or derivative, metformin and a sulfonylurea; an insulin analogue or derivative and troglitazone; an insulin analogue or derivative and pioglitazone; an insulin analogue or derivative and an insulin sensitizer such as disclosed in WO 00/63189 or WO 97/41097; an insulin analogue or derivative and lovastatin; etc.

Furthermore, the compounds according to the invention may be administered in combination with one or more antiobesity agents or appetite regulating agents.

Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4 (melanocortin 4) agonists, orexin antagonists, TNF (tumor necrosis factor) modulators, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, urocortin agonists, β3 adrenergic agonists such as CL-316243, AJ-9677, GW-0604, LY362884, LY377267 or AZ-40140, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, serotonin re-uptake inhibitors such as fluoxetine, seroxat or citalopram, serotonin and noradrenaline re-uptake inhibitors, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing compounds, TRH (thyreotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA (dopamine) agonists (bromocriptin, doprexin), lipase/amylase inhibitors, PPAR modulators, RXR modulators or TR β agonists.

In one embodiment of the invention the antiobesity agent is leptin.

In another embodiment of the invention the antiobesity agent is dexamphetamine or amphetamine.

In another embodiment of the invention the antiobesity agent is fenfluramine or dexfenfluramine.

In still another embodiment of the invention the antiobesity agent is sibutramine.

In a further embodiment of the invention the antiobesity agent is orlistat.

In another embodiment of the invention the antiobesity agent is mazindol or phentermine.

Furthermore, the present compounds may be administered in combination with one or more antihypertensive agents. Examples of antihypertensive agents are β-blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem and verapamil, and α-blockers such as doxazosin, urapidil, prazosin and terazosin. Further reference can be made to Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

It should be understood that any suitable combination of the compounds according to the invention with diet and/or exercise, one or more of the above-mentioned compounds and optionally one or more other active substances are considered to be within the scope of the present invention.

PHARMACEUTICAL COMPOSITIONS

The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, they can

be prepared with coatings such as enteric coatings or they can be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well known in the art.

Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and non-aqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot injectable formulations are also contemplated as being within the scope of the present invention.

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants etc.

A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body weight per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day administered in one or more dosages such as 1 to 3 dosages. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration one or more times per day such as 1 to 3 times per day may contain from 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg, and more preferred from about 0.5 mg to about 200 mg.

For parenteral routes such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is a base addition salt of a compound having the utility of a free acid. When a compound of the formula (I) contains a free acid such salts are

prepared in a conventional manner by treating a solution or suspension of a free acid of the formula (I) with a chemical equivalent of a pharmaceutically acceptable base. Representative examples are mentioned above.

For parenteral administration, solutions of the novel compounds of the formula (I) in sterile aqueous solution, aqueous propylene glycol, aqueous vitamin E or sesame or peanut oil may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatine, agar, pectin, acacia, magnesium stearate, stearic acid and lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethylene and water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The pharmaceutical compositions formed by combining the novel compounds of the formula (I) and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include a suitable excipient. Furthermore, the orally available formulations may be in the form of a powder or granules, a solution or suspension in an aqueous or non-aqueous liquid, or an oil-in-water or water-in-oil liquid emulsion.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gela-

tine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

A typical tablet that may be prepared by conventional tabletting techniques may contain:

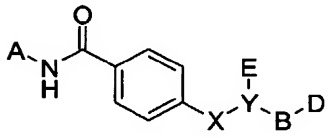
Core:		
Active compound (as free compound or salt thereof)		5.0 mg
Lactosum Ph. Eur.		67.8 mg
Cellulose, microcryst. (Avicel)		31.4 mg
Amberlite®IRP88*		1.0 mg
Magnesii stearas Ph. Eur.		q.s.
Coating:		
Hydroxypropyl methylcellulose	approx.	9 mg
Mywacett 9-40 T**	approx.	0.9 mg

* Polacrillin potassium NF, tablet disintegrant, Rohm and Haas.

** Acylated monoglyceride used as plasticizer for film coating.

If desired, the pharmaceutical composition of the invention may comprise the compound of the formula (I) in combination with further pharmacologically active substances such as those described below.

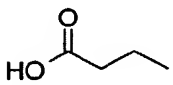
In an aspect of the invention the compound is represented by the general formula (I)



(I)

wherein

A is



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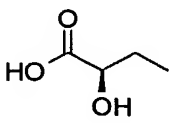

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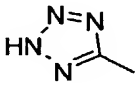


,

X is a valence bond, $-CR^1R^2-$ or $-NR^1-$,

Y is $>CR^3-$ or $>N-$,

R^1, R^2 and R^3 independently are hydrogen or C_{1-6}-alkyl, or R^1 and R^3 on adjacent atoms may be combined to form a double bond,

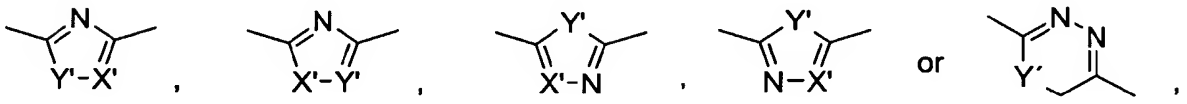
E is

- C_{1-10}-alkyl or C_{2-10}-alkenyl,

- C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, C_{7-10}-bicycloalkyl, C_{3-10}-cycloalkyl-C_{1-6}-alkyl, C_{3-10}-cycloalkenyl-C_{1-6}-alkyl or C_{7-10}-bicycloalkyl-C_{1-6}-alkyl, wherein the rings may optionally be substituted with one or more substituents selected from halogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{1-6}-alkoxy, C_{1-6}-thioalkyl, $-CF_3$, $-OCF_3$, $-SCF_3$, $-OCHF_2$ and $-SCHF_2$,

- aryl, aryloxy, arylthio, heteroaryl, aryl-C_{1-6}-alkyl, aryloxy-C_{1-6}-alkyl, arylthio-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, diaryl-C_{1-6}-alkyl or (C_{1-6}-alkyl)(aryl)-C_{1-7}-alkyl, wherein the non-aromatic and aromatic rings may optionally be substituted with one or more substituents selected from halogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{1-6}-alkoxy, C_{1-6}-thioalkyl, $-CF_3$, $-OCF_3$, $-SCF_3$, $-OCHF_2$, $-SCHF_2$, C_{3-10}-cycloalkyl and C_{3-10}-cycloalkenyl, or with two substituents on adjacent positions which are combined to form a bridge C_{1-6}-alkylene, C_{2-6}-alkenylene or $-O-C_{1-6}$-alkylene-O-,

B is



X' is $-N=$ or $-CR^8=$,

Y' is -S-, -O- or $-NR^9-$,

R^8 is hydrogen, C_{1-6}-alkyl or aryl, wherein aryl is optionally substituted with one or two substituents selected from halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-thioalkyl, $-CF_3$, $-OCF_3$, $-SCF_3$, $-OCHF_2$, $-SCHF_2$, $-SO_2CF_3$ and $-SO_2-C_{1-6}$-alkyl,

R^9 is hydrogen or C_{1-6}-alkyl,

D is aryl or heteroaryl,

which may optionally be substituted with one or more substituents selected from

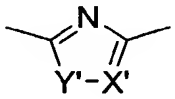
- halogen, $-CF_3$, $-OCF_3$, $-SCF_3$, $-CN$, $-NO_2$, C_{1-10}-alkyl, C_{2-6}-alkenyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, amino, C_{1-6}-alkylamino, di-C_{1-6}-alkylamino, $-SO_2CF_3$ and $-SO_2-C_{1-6}$-alkyl,

- C_{3-8}-cycloalkyl, C_{3-8}-cycloalkenyl, aryl and aryl-C_{1-6}-alkoxy, wherein the non-aromatic and aromatic rings optionally may be substituted with one to three substituents selected from halogen, $-CF_3$, $-OCF_3$, $-SCF_3$, $-CN$, $-NO_2$, C_{1-10}-alkyl, C_{2-6}-alkenyl, C_{1-6}-alkoxy and C_{1-6}-alkylthio, or with two substituents on adjacent positions which are combined to form a bridge $-O-(CH_2)_m-O-(CH_2)_p-$ or $-O-(CF_2)_m-O-(CF_2)_p-$, wherein m is an integer of from 1 to 6, and p is 0 or 1,

- or with two substituents on adjacent positions which are combined to form a bridge $-O-(CH_2)_m-O-(CH_2)_p-$ or $-O-(CF_2)_m-O-(CF_2)_p-$, wherein m is an integer of from 1 to 6, and p is 0 or 1,

or a substituent on B may be combined with a substiuent on D to form a –C(=O)- bridge, as well as any diastereomer or enantiomer or tautomeric form thereof including mixtures of these.

In one embodiment the invention provides the compounds as above, wherein B is



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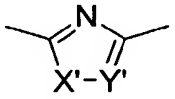
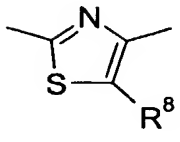


,

wherein X' and Y' are as defined above.

In another embodiment the invention provides the compounds as above, wherein B is

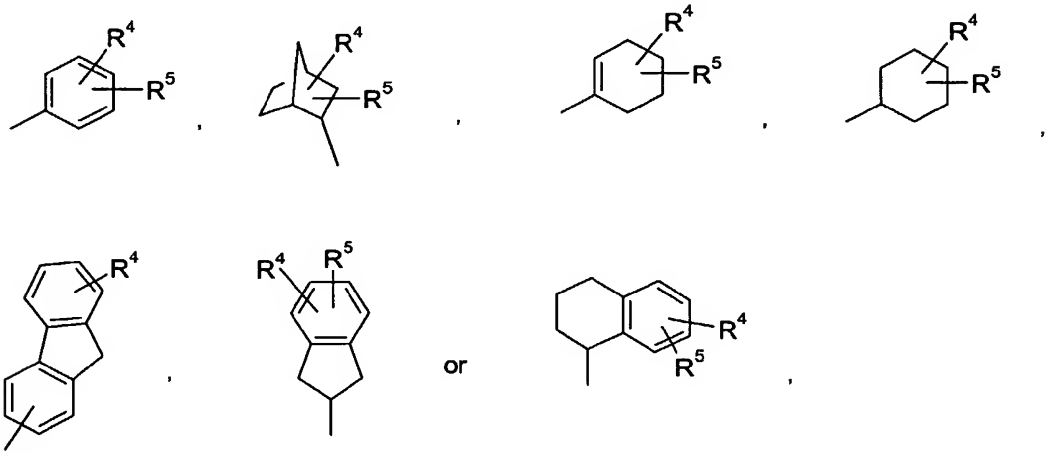


wherein R^8 is as defined above.

In another embodiment the invention provides the compounds as above, wherein E is

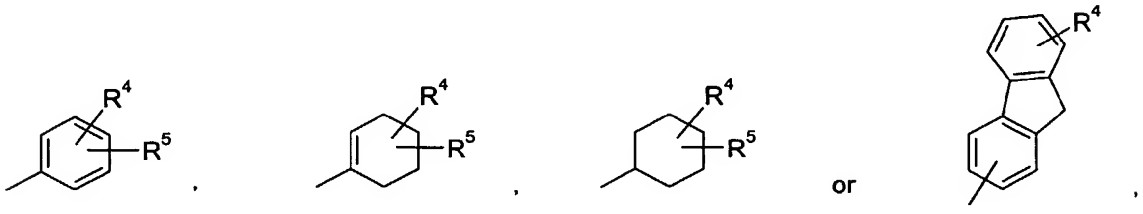
C_{1-10}-alkyl,

C_{3-10}-cycloalkyl, which may optionally be substituted as defined above.



wherein R^4 and R^5 are as defined above.

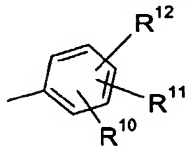
In another embodiment the invention provides the compounds as above, wherein E is



wherein R^4 is hydrogen and R^5 is C_{1-6}-alkyl, C_{1-6}-alkoxy, cyclohexyl, halogen, $-CF_3$ or cyclohex-1-enyl,

or R^4 and R^5 on adjacent positions may be combined to form a bridge C_{1-6}-alkylene.

In another embodiment the invention provides the compounds as above, wherein D is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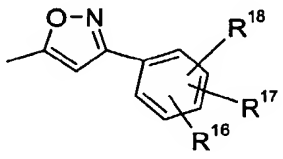
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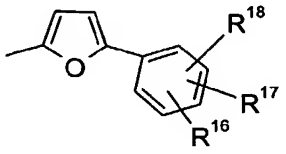
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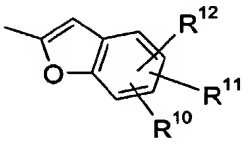
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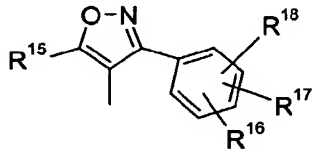
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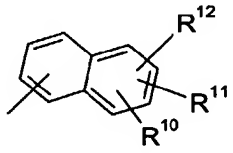
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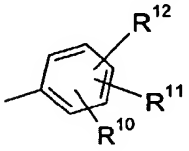
wherein R^{10}, R^{11}, R^{12}, R^{15}, R^{16}, R^{17} and R^{18} are as defined above.

In another embodiment the invention provides the compounds as above, wherein D is


,

wherein R^{10}, R^{11} and R^{12} are as defined above.

In another embodiment the invention provides the compounds as above, wherein R^{10}, R^{11} and R^{12} independently are hydrogen, halogen, $-OCF_3$, $-CF_3$, $-NO_2$, di-C_{1-6}-alkylamino, C_{1-10}-alkyl, C_{1-6}-alkoxy or -CN,

phenyl or phenyl-C_{1-6}-alkoxy,

or two of R^{10}, R^{11} and R^{12} in adjacent positions form a bridge $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$ or $-O-CH_2-CH_2-CH_2-O-$.

In another embodiment the invention provides the compounds as above, wherein one of R^{10}, R^{11} and R^{12} represent hydrogen.

In another embodiment the invention provides the compounds as above, wherein one or two of R^{10}, R^{11} and R^{12} is hydrogen, and the remaining is independently selected from halogen, $-OCF_3$, $-CF_3$, $-NO_2$, di-C_{1-6}-alkylamino, C_{1-10}-alkyl, C_{1-6}-alkoxy or –CN.

In another embodiment the invention provides the compounds such as

3-(4-{[[4-(4-Chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)amino]methyl}benzoylamino)-propionic acid,

3-(4-{[[4-(3,4-Dichlorophenyl)thiazol-2-yl]-(5,6,7,8-tetrahydronaphthalen-2-yl)amino]methyl}-benzoylamino)propionic acid

3-[4-({(4-Chlorophenyl)-[4-(4-trifluoromethoxyphenyl)thiazol-2-yl]amino}methyl)benzoyl-amino]propionic acid,3-[4-({(4-Chlorophenyl)-[4-(4-trifluoromethylphenyl)thiazol-2-yl]amino}methyl)benzoylamino]propionic acid or

3-[4-({(4-Trifluoromethoxyphenyl)-[4-(4-trifluoromethylphenyl)thiazol-2-yl]amino}methyl)-benzoylamino]propionic acid,

In another embodiment the invention provides the compounds such as 3-(4-{[[4-(3,4-Dichlorophenyl)thiazol-2-yl]-(5,6,7,8-tetrahydronaphthalen-2-yl)amino]methyl}-benzoylamino)propionic acid as a salt with tert-butylamine.

In another embodiment the invention provides the compound 3-(4-{[[4-(4-chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)amino]methyl}benzoylamino)propionic acid as a salt with L-lysine.

In another embodiment the invention provides the compound3-(4-{[[4-(4-chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)amino]methyl}benzoylamino)propionic acid as a salt with L-histidine.

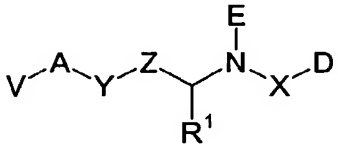
In another embodiment the invention provides the compound3-(4-{[[4-(4-chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)amino]methyl}benzoylamino)propionic acid as a salt with monoethanolamine.

In another embodiment the invention provides the compound3-(4-{[[4-(4-chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)amino]methyl}benzoylamino)propionic acid as a salt with tert-butylamine.

In another embodiment the invention provides the compound3-(4-{[[4-chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)amino]methyl}benzoylamino)propionic acid as a salt with 1,2-ethylenediamine.

In another embodiment the invention provides the compound 3-(4-{[[4-(4-chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)amino]methyl}benzoylamino)propionic acid as a salt with N,N'-dibenzylethylenediamine.

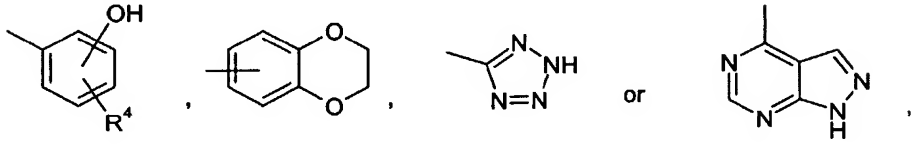
In an embodiment the invention provides glucagon antagonists of the formula (I):



(I)

wherein

V is $-C(O)OR^2$, $-C(O)NR^2R^3$, $-C(O)NR^2OR^3$, $-S(O)_2OR^2$,



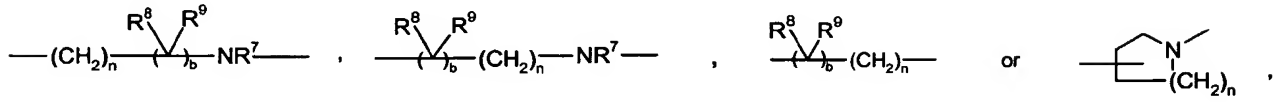
wherein

R^2 and R^3 independently are hydrogen or C_{1-6}-alkyl,

R^4 is hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^5$, $-NR^5R^6$ or C_{1-6}-alkyl,

wherein R^5 and R^6 independently are hydrogen or C_{1-6}-alkyl,

A is



wherein

b is 0 or 1,

n is 0, 1, 2 or 3,

R^7 is hydrogen, C_{1-6}-alkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,

R^8 and R^9 independently are hydrogen or C_{1-6}-alkyl,

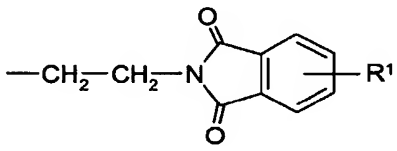
Y is -C(O)-, -$S(O)_2$-, -O- or a valence bond,

Z is phenylene or a divalent radical derived from a 5 or 6 membered heteroaromatic ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur,

which may optionally be substituted with one or two groups R^{46} and R^{47} selected from hydrogen, halogen, -CN, -CF_3, -OCF_3, -NO_2, -OR^{10}, -$NR^{10}R^{11}$ and C_{1-6}-alkyl,

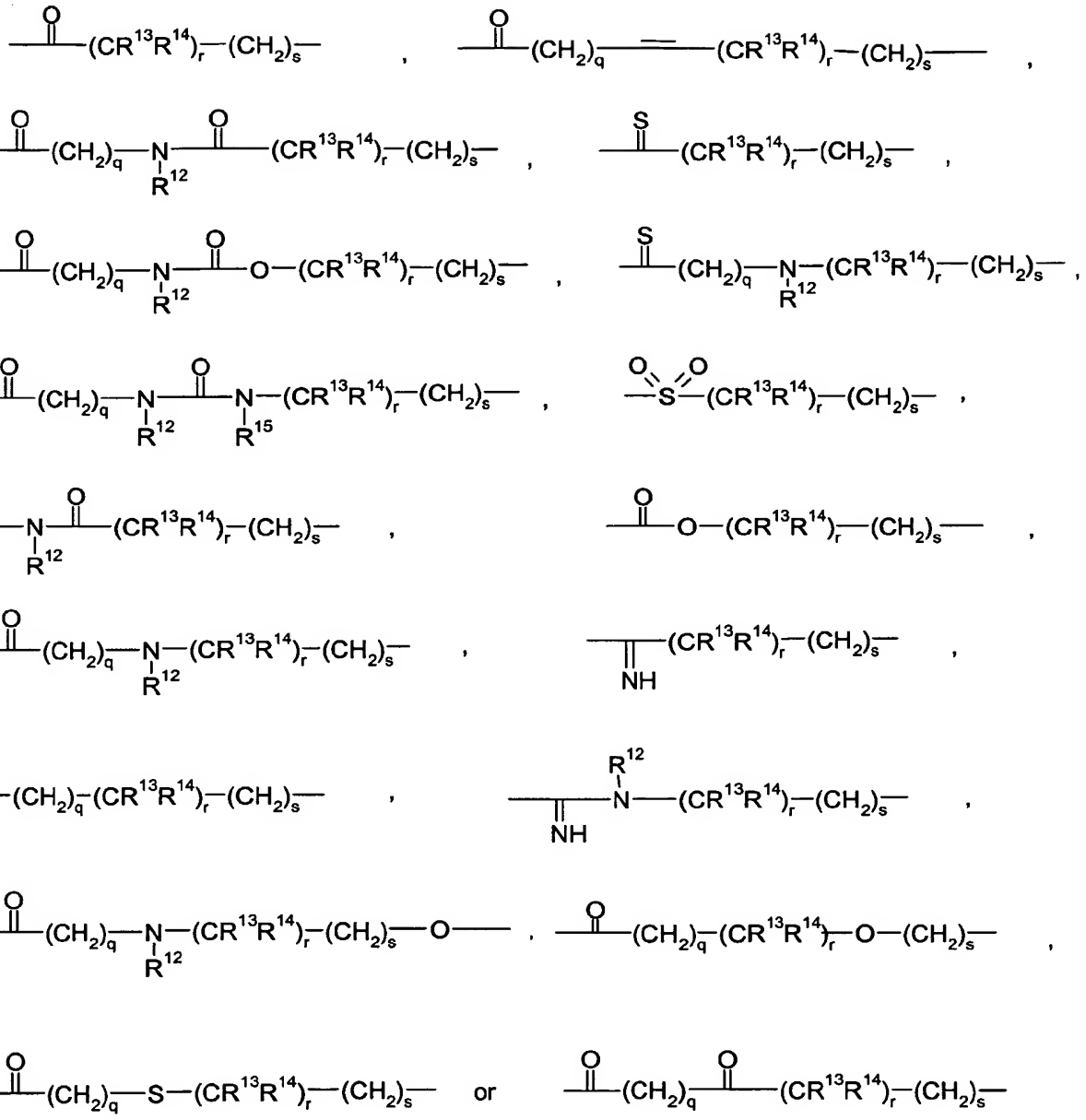
wherein R^{10} and R^{11} independently are hydrogen or C_{1-6}-alkyl,

or -A-Y-Z- together are



R^1 is hydrogen or C_{1-6}-alkyl,

X is



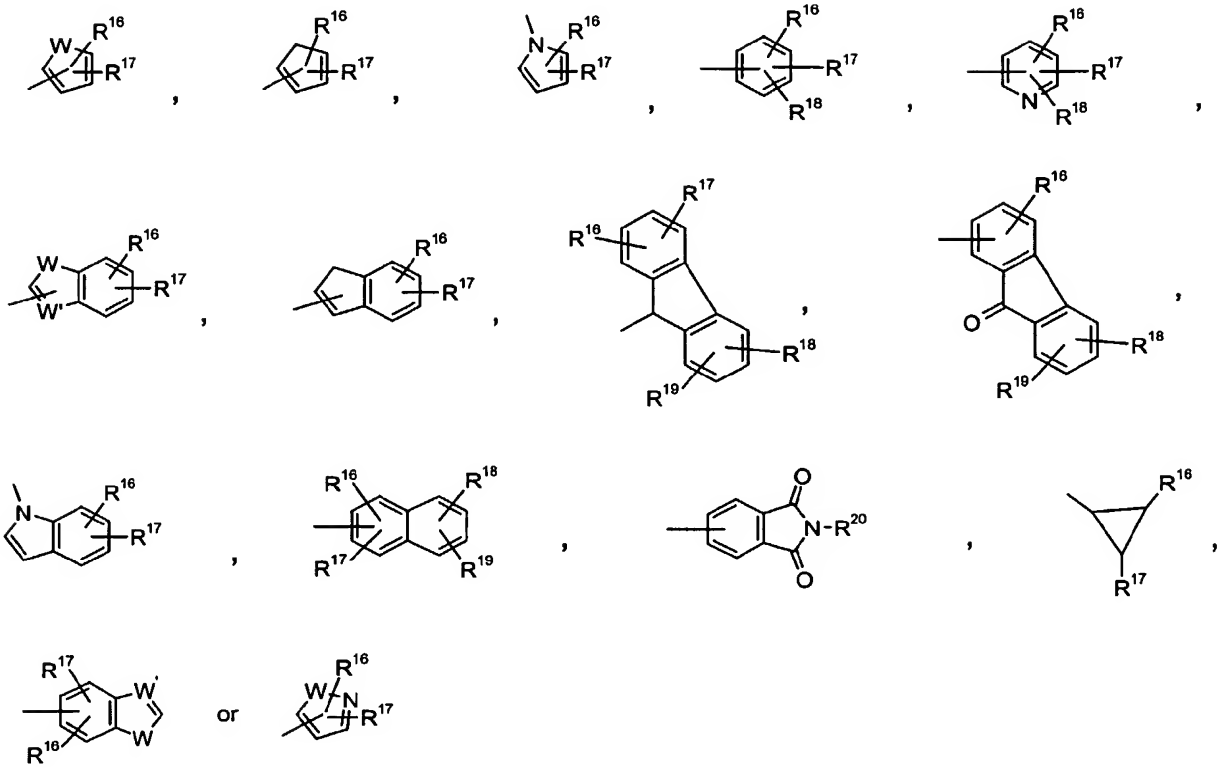
wherein

r is 0 or 1,

q and s independently are 0, 1, 2 or 3,

R^{12}, R^{13}, R^{14} and R^{15} independently are hydrogen or C_{1-6}-alkyl,

D is



wherein

W is -O-, -S-, -$S(O)_2$- or -NR^{20}-,

W' is =$CR^{20'}$- or =N-,

R^{16}, R^{17}, R^{18} and R^{19} independently are

- hydrogen, halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$OS(O)_2CF_3$, -SCF_3, -NO_2, -OR^{21}, -$NR^{21}R^{22}$, -SR^{21}, -$NR^{21}S(O)_2R^{22}$, -$S(O)_2NR^{21}R^{22}$, -$S(O)NR^{21}R^{22}$, -$S(O)R^{21}$, -$S(O)_2R^{21}$, -$OS(O)_2R^{21}$, -$C(O)NR^{21}R^{22}$, -$OC(O)NR^{21}R^{22}$, -$NR^{21}C(O)R^{22}$, -$CH_2C(O)NR^{21}R^{22}$, -$OCH_2C(O)NR^{21}R^{22}$, -CH_2OR^{21}, -$CH_2NR^{21}R^{22}$, -$OC(O)R^{21}$, -$C(O)R^{21}$ or -$C(O)OR^{21}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

  which may optionally be substituted with one or more substituents selected from -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -SCF_3, -OR^{21}, -$NR^{21}R^{22}$, -SR^{21}, -$S(O)R^{21}$, -$S(O)_2R^{21}$, -$C(O)NR^{21}R^{22}$, -$OC(O)NR^{21}R^{22}$, -$NR^{21}C(O)R^{22}$, -$OCH_2C(O)NR^{21}R^{22}$, -$C(O)R^{21}$ and -$C(O)OR^{21}$,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkoxy, C_{3-8}-cycloalkyloxy, C_{3-8}-cycloalkyl-C_{1-6}-alkylthio, C_{3-8}-cycloalkylthio, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl or heterocyclyl-C_{2-6}-alkynyl,

  of which the cyclic moieties optionally may be substituted with one or more substituents selected from

  -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -SCF_3, -OR^{21}, -$NR^{21}R^{22}$, -SR^{21}, -$S(O)R^{21}$, -$S(O)_2R^{21}$, -$C(O)NR^{21}R^{22}$, -$OC(O)NR^{21}R^{22}$, -$NR^{21}C(O)R^{22}$, -$OCH_2C(O)NR^{21}R^{22}$, -$C(O)R^{21}$ and -$C(O)OR^{21}$,

  C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl,

    which may optionally be substituted with one or more substituents selected from -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -SCF_3, -OR^{21}, -$NR^{21}R^{22}$, -SR^{21}, -$S(O)R^{21}$, -$S(O)_2R^{21}$, -$C(O)NR^{21}R^{22}$, -$OC(O)NR^{21}R^{22}$, -$NR^{21}C(O)R^{22}$, -$OCH_2C(O)NR^{21}R^{22}$, -$C(O)R^{21}$ and -$C(O)OR^{21}$,

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

  of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from

halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$OS(O)_2CF_3$, -SCF_3, -NO_2, -OR^{21}, -$NR^{21}R^{22}$, -SR^{21}, -$NR^{21}S(O)_2R^{22}$, -$S(O)_2NR^{21}R^{22}$, -$S(O)NR^{21}R^{22}$, -$S(O)R^{21}$, -$S(O)_2R^{21}$, -$OS(O)_2R^{21}$, -$C(O)NR^{21}R^{22}$, -$OC(O)NR^{21}R^{22}$, -$NR^{21}C(O)R^{22}$, -$CH_2C(O)NR^{21}R^{22}$, -$OCH_2C(O)NR^{21}R^{22}$, -CH_2OR^{21}, -$CH_2NR^{21}R^{22}$, -$OC(O)R^{21}$, -$C(O)R^{21}$ and -$C(O)OR^{21}$,

C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -SCF_3, -OR^{21}, -$NR^{21}R^{22}$, -SR^{21}, -$S(O)R^{21}$, -$S(O)_2R^{21}$, -$C(O)NR^{21}R^{22}$, -$OC(O)NR^{21}R^{22}$, -$NR^{21}C(O)R^{22}$, -$OCH_2C(O)NR^{21}R^{22}$, -$C(O)R^{21}$ and -$C(O)OR^{21}$,

wherein R^{21} and R^{22} independently are hydrogen, -CF_3, C_{1-6}-alkyl, tri-C_{1-6}-alkylsilyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, aryl, aryl-C_{1-6}-alkyl or heteroaryl,

or R^{21} and R^{22} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{16} to R^{19} when placed in adjacent positions together may form a bridge –$(CR^{16'}R^{17'})_a$-O-$(CR^{18'}R^{19'})_c$-O-,

wherein

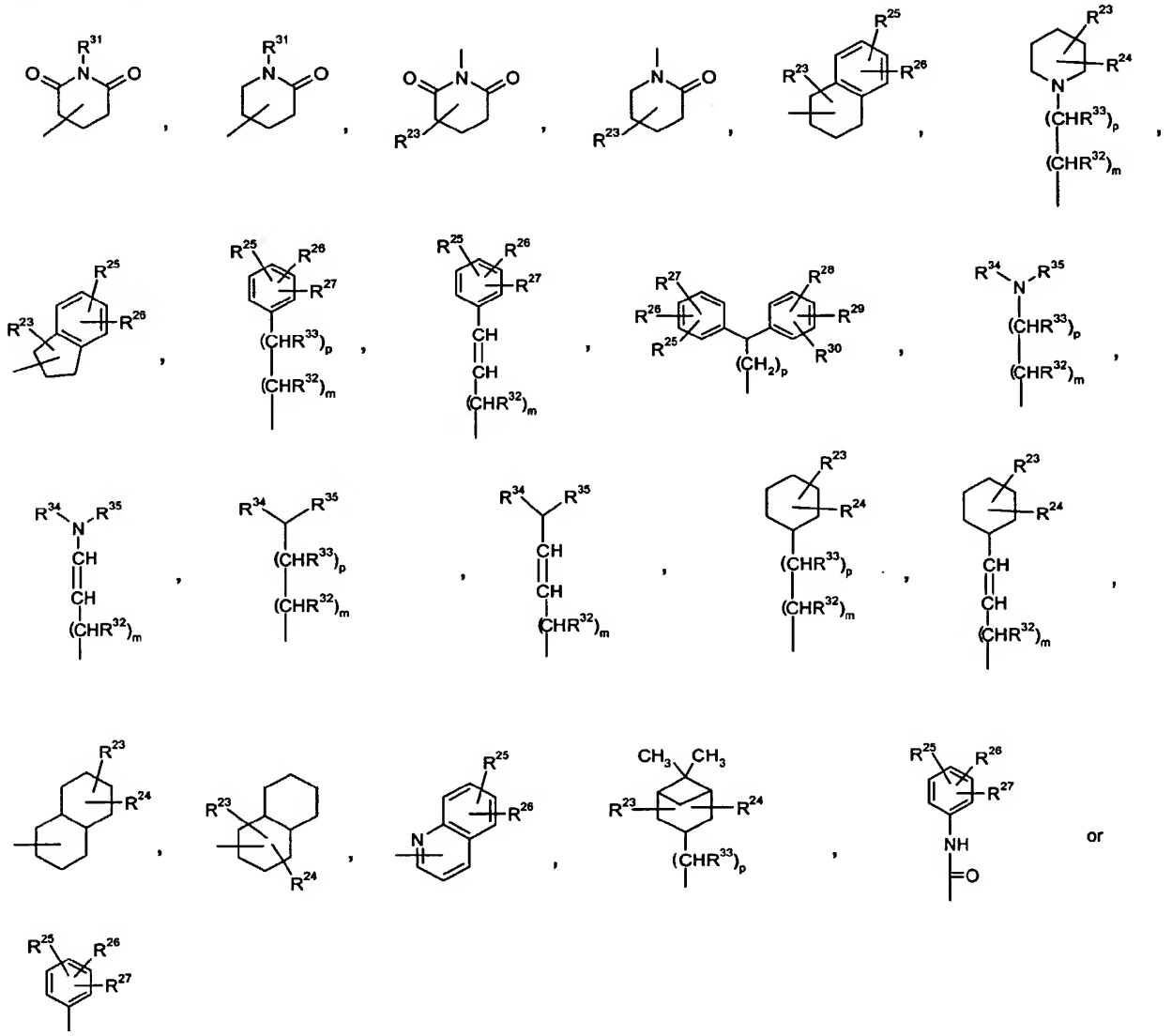
a is 0, 1 or 2,

c is 1 or 2,

$R^{16'}$, $R^{17'}$, $R^{18'}$ and $R^{19'}$ independently are hydrogen, C_{1-6}-alkyl or halogen,

R^{20} and $R^{20'}$ independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,

E is a 3 to 9 membered mono- or bicyclic ring which may optionally contain one or two double bonds and which may optionally contain one or two heteroatoms selected from nitrogen, oxygen and sulfur, wherein one or two groups R^{23} and R^{24} may be attached to the same or different ring carbon atoms and wherein a group R^{31} may be attached to a ring nitrogen atom when present, or



wherein

m and p independently are 0, 1, 2, 3 or 4, with the proviso that when both m and p are present in the same formula at least one of m and p is different from 0,

R^{23} and R^{24} independently are

- hydrogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{36}$, $-NR^{36}R^{37}$, $-SR^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-C(O)NR^{36}R^{37}$, $-OC(O)NR^{36}R^{37}$, $-NR^{36}C(O)R^{37}$, $-OCH_2C(O)NR^{36}R^{37}$, $-C(O)R^{36}$ or $-C(O)OR^{36}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

  which may optionally be substituted with one or more substituents selected from $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{36}$, $-NR^{36}R^{37}$, $-SR^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-C(O)NR^{36}R^{37}$, $-OC(O)NR^{36}R^{37}$, $-NR^{36}C(O)R^{37}$, $-OCH_2C(O)NR^{36}R^{37}$, $-C(O)R^{36}$ and $-C(O)OR^{36}$,

- C_{3-8}-cycloalkyl, C_{3-8}-cycloalkylidene, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl or heterocyclyl-C_{2-6}-alkynyl,

  of which the cyclic moieties optionally may be substituted with one or more substituents selected from

  $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{36}$, $-NR^{36}R^{37}$, $-SR^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-C(O)NR^{36}R^{37}$, $-OC(O)NR^{36}R^{37}$, $-NR^{36}C(O)R^{37}$, $-OCH_2C(O)NR^{36}R^{37}$, $-C(O)R^{36}$ and $-C(O)OR^{36}$,

  C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl,

  which may optionally be substituted with one or more substituents selected from $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{36}$, $-NR^{36}R^{37}$, $-SR^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-C(O)NR^{36}R^{37}$, $-OC(O)NR^{36}R^{37}$, $-NR^{36}C(O)R^{37}$, $-OCH_2C(O)NR^{36}R^{37}$, $-C(O)R^{36}$ and $-C(O)OR^{36}$,

- aryl, aryloxy, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from

halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$OS(O)_2CF_3$, -SCF_3, -NO_2, -OR^{36}, -$NR^{36}R^{37}$, -SR^{36}, -$NR^{36}S(O)_2R^{37}$, -$S(O)_2NR^{36}R^{37}$, -$S(O)NR^{36}R^{37}$, -$S(O)R^{36}$, -$S(O)_2R^{36}$, -$OS(O)_2R^{36}$, -$C(O)NR^{36}R^{37}$, -$OC(O)NR^{36}R^{37}$, -$NR^{36}C(O)R^{37}$, -$CH_2C(O)NR^{36}R^{37}$, -$CH_2C(O)NR^{36}R^{37}$, -CH_2OR^{36}, -$CH_2NR^{36}R^{37}$, -$OC(O)R^{36}$, -$C(O)R^{36}$ and -$C(O)OR^{36}$,

C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -SCF_3, -OR^{36}, -$NR^{36}R^{37}$, -SR^{36}, -$S(O)R^{36}$, -$S(O)_2R^{36}$, -$C(O)NR^{36}R^{37}$, -$OC(O)NR^{36}R^{37}$, -$NR^{36}C(O)R^{37}$, -$OCH_2C(O)NR^{36}R^{37}$, -$C(O)R^{36}$ and -$C(O)OR^{36}$,

wherein R^{36} and R^{37} independently are hydrogen, C_{1-6}-alkyl or aryl,

of which the aryl moiety optionally may be substituted with one or more substituents selected from halogen, -CN, -CF_3, -OCF_3, -NO_2, -OR^{38}, -$NR^{38}R^{39}$ and C_{1-6}-alkyl,

wherein R^{38} and R^{39} independently are hydrogen or C_{1-6}-alkyl,

or R^{36} and R^{37} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or R^{23} and R^{24} when attached to the same ring carbon atom or different ring carbon atoms together may form a radical -O-$(CH_2)_t$-$CR^{40}R^{41}$-$(CH_2)_l$-O-, -$(CH_2)_t$-$CR^{40}R^{41}$-$(CH_2)_l$- or

$-S-(CH_2)_t-CR^{40}R^{41}-(CH_2)_l-S-$,

wherein

t and l independently are 0, 1, 2, 3, 4 or 5,

R^{40} and R^{41} independently are hydrogen or C_{1-6}-alkyl,

R^{25} to R^{30} independently are hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{42}$, $-NR^{42}R^{43}$, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl,

wherein R^{42} and R^{43} independently are hydrogen or C_{1-6}-alkyl, or

R^{42} and R^{43} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

R^{31}, R^{32} and R^{33} independently are hydrogen or C_{1-6}-alkyl,

R^{34} and R^{35} independently are

- hydrogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkanoyl, $-C(O)NR^{44}R^{45}$ or $-S(O)_2R^{45}$,
- aryl, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkanoyl or aryl-C_{1-6}-alkyl,

  of which the aryl moieties optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{44}$, $-NR^{44}R^{45}$ and C_{1-6}-alkyl,

wherein R^{44} and R^{45} independently are hydrogen or C_{1-6}-alkyl, or

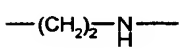
R^{34} and R^{35} when attached to a carbon atom together with the said carbon atom may form a 3 to 8 membered cyclic ring optionally containing one or two heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds, or

R^{34} and R^{35} when attached to a nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds,

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these.

In an embodiment the invention provides compounds, wherein V is -C(O)OH or 5-tetrazolyl.

In an embodiment the invention provides compounds, wherein A is



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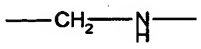

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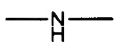

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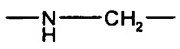
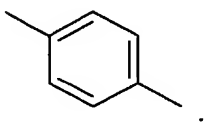


In an embodiment the invention provides compounds, wherein Y is -C(O)-,

or Y is a valence bond.

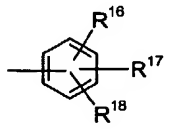
In an embodiment the invention provides compounds,wherein Z is



In an embodiment the invention provides compounds, wherein R^1 is hydrogen or methyl.

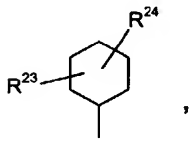
In an embodiment the invention provides compounds, wherein X is -C(O)NH-, -C(O)NHCH$_2$-, -C(O)NHCH(CH$_3$)-, -C(O)NHCH$_2$CH$_2$-, -C(O)CH$_2$-, -CH$_2$-, -C(O)- or -NHC(O)-.

In an embodiment the invention provides compounds, wherein D is



wherein one or two of R^{16}, R^{17}, and R^{18} are hydrogen and the remaining is independently selected from -OCF$_3$, -SCF$_3$ -CF$_3$, –S(O)$_2$CH$_3$, phenyl, halogen, C$_{1-6}$-alkyl, nitro, -S-C$_{1-6}$-alkyl or -S(O)$_2$NR^{21}R^{22}, wherein R^{21} is C$_{1-6}$-alkyl and R^{22} is phenyl.

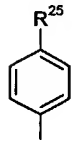
In an embodiment the invention provides compounds, wherein E is



,

wherein R^{23} is hydrogen and R^{24} is C$_{1-6}$-alkyl such as *tert*-butyl or C$_{3-8}$-cycloalkyl such as cyclohexyl, wherein R^{23} and R^{24} are both C$_{1-6}$-alkyl or wherein R^{23} and R^{24} together form the radical –(CH$_2$)$_5$-.

In an embodiment the invention provides compounds, wherein E is



,

wherein R^{25} is –OCF$_3$, -CF$_3$, C$_{1-6}$-alkyl such as *tert*-butyl, phenyl, piperidyl, C$_{3-8}$-cycloalkyl such as cyclohexyl or C$_{4-8}$-cycloalkenyl such as cyclohexenyl.

In an embodiment the invention provides compounds, wherein the compound is any of the following

3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-propionic acid,

4-[3-(3,5-Bistrifluoromethylphenyl)-1-(4-tert-butylcyclohexyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide,

(S)-4-[3-[1-(4-Chlorophenyl)ethyl]-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide,

4-[1-(4-Cyclohexylphenyl)-3-(3-fluoro-5-trifluoromethylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

4-[3-(3-Bromo-5-trifluoromethylphenyl)-1-(4-*tert*-butylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide,

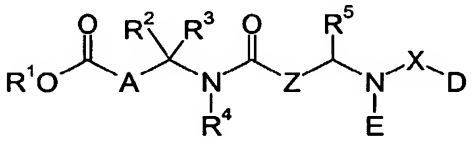
4-[3-(3-Bromo-5-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide,

4-[3-(3-Bromophenyl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide.

In an embodiment the invention provides the compound N-[4-({4-(1-cyclohexen-1-yl)[(3,5-dichloroanilino)carbonyl]anilino}methyl)benzoyl]-*β*-alanine as a salt with and tert-butylamine.

In an embodiment the invention provides the compound N-[4-({4-(1-cyclohexen-1-yl)[(3,5-dichloroanilino)carbonyl]anilino}methyl)benzoyl]-*β*-alanine as a salt with L-arginine.

In an embodiment the invention provides a glucagon antagonist represented by the general formula (I):



(I)

wherein

R^1, R^2, R^3, R^4 and R^5 independently are hydrogen or C_{1-6}-alkyl,

A is -C(O)-, -CH(OR^6)- or –CHF-,

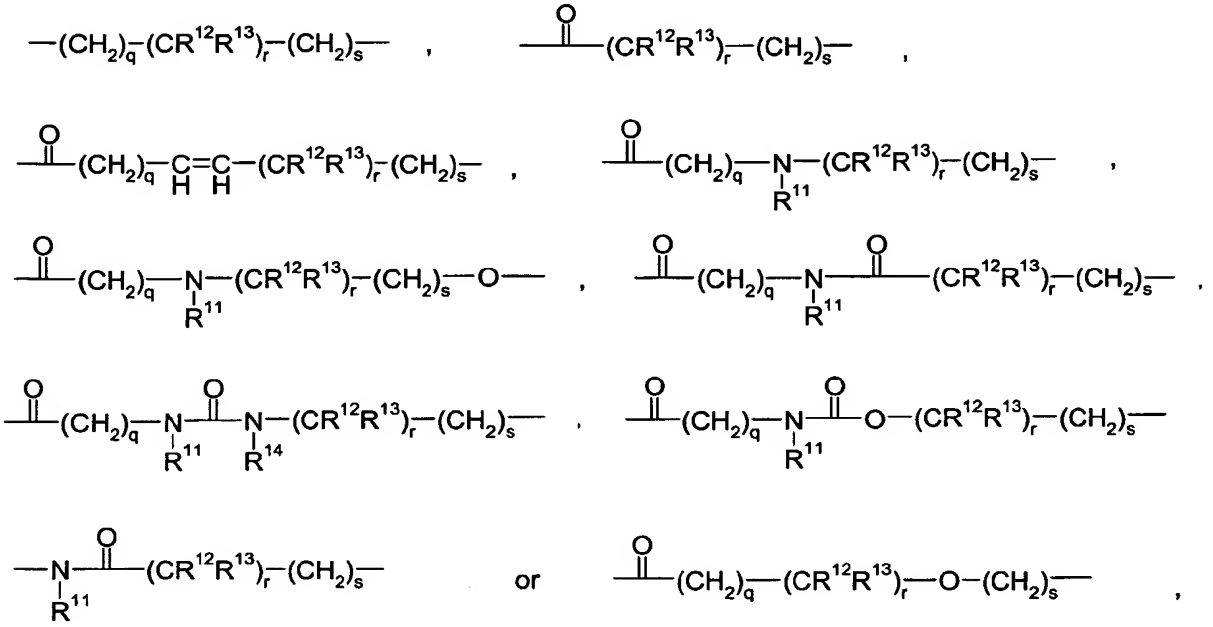
wherein R^6 is hydrogen or C_{1-6}-alkyl,

Z is arylene or a divalent radical derived from a 5 or 6 membered heteroaromatic ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur,

which may optionally be substituted with one or two groups R^7 and R^8 selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^9$, $-NR^9R^{10}$ and C_{1-6}-alkyl,

wherein R^9 and R^{10} independently are hydrogen or C_{1-6}-alkyl,

X is



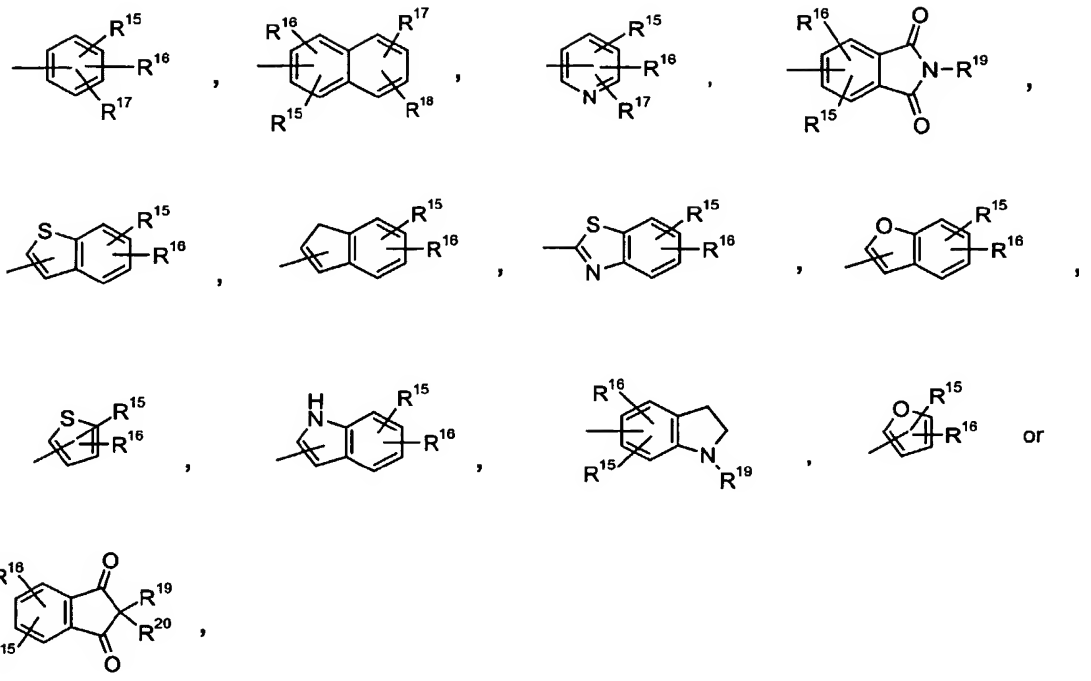
wherein

r is 0 or 1,

q and s independently are 0, 1, 2 or 3,

R^{11}, R^{12}, R^{13} and R^{14} independently are hydrogen, C_{1-6}-alkyl or C_{3-8}-cycloalkyl,

D is



wherein

R^{15}, R^{16}, R^{17} and R^{18} independently are

- hydrogen, halogen, -CN, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{21}$, $-NR^{21}R^{22}$, $-SR^{21}$, $-NR^{21}S(O)_2R^{22}$, $-S(O)_2NR^{21}R^{22}$, $-S(O)NR^{21}R^{22}$, $-S(O)R^{21}$, $-S(O)_2R^{21}$, $-C(O)NR^{21}R^{22}$, $-OC(O)NR^{21}R^{22}$, $-NR^{21}C(O)R^{22}$, $-CH_2C(O)NR^{21}R^{22}$, $-OCH_2C(O)NR^{21}R^{22}$, $-OC(O)R^{21}$, $-C(O)R^{21}$ or $-C(O)OR^{21}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

  which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{21}$, $-NR^{21}R^{22}$ and C_{1-6}-alkyl,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkoxy, C_{3-8}-cycloalkyloxy, C_{3-8}-cycloalkyl-C_{1-6}-alkylthio, C_{3-8}-cycloalkylthio, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl,

C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, $-C(O)OR^{21}$, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{21}$, $-NR^{21}R^{22}$ and C_{1-6}-alkyl,

wherein R^{21} and R^{22} independently are hydrogen, C_{1-6}-alkyl, aryl-C_{1-6}-alkyl or aryl,

or R^{21} and R^{22} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{15} to R^{18} when placed in adjacent positions together may form a bridge $-(CR^{23}R^{24})_a$-O-$(CR^{25}R^{26})_c$-O-,

wherein

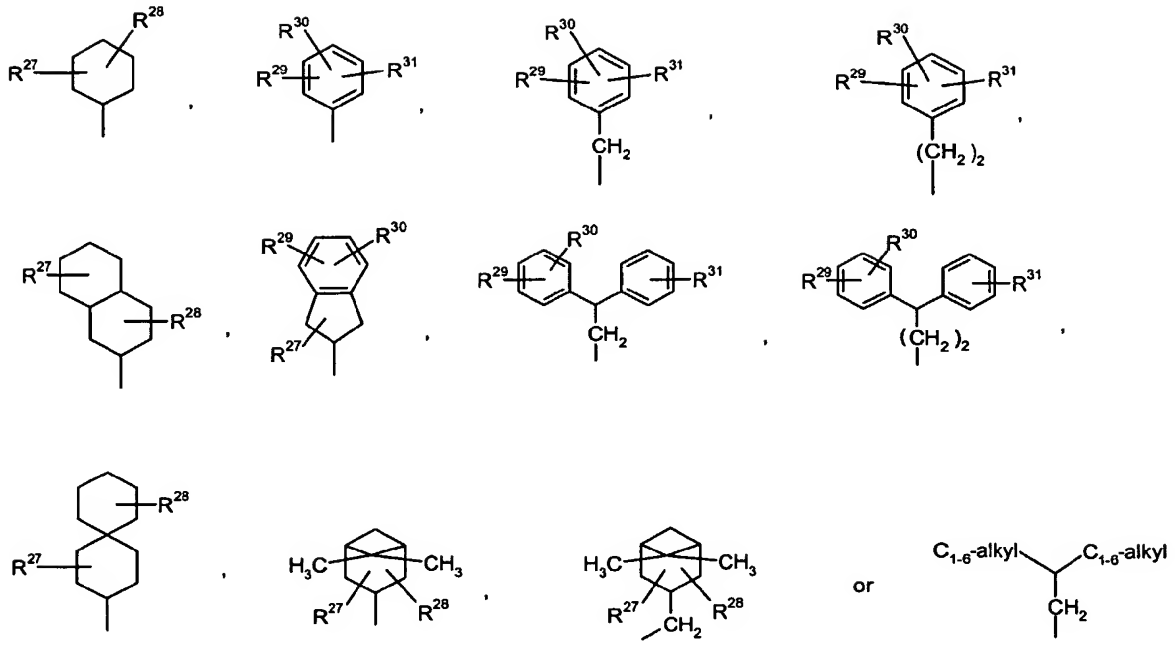
a is 0, 1 or 2,

c is 1 or 2,

R^{23}, R^{24}, R^{25} and R^{26} independently are hydrogen, C_{1-6}-alkyl or fluorine,

R^{19} and R^{20} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,

E is



wherein

R^{27} and R^{28} independently are

hydrogen, halogen, -CN, $-CF_3$, $-OR^{32}$, $-NR^{32}R^{33}$, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl or aryl,

wherein the aryl group optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{32}$, $-NR^{32}R^{33}$ and C_{1-6}-alkyl,

wherein R^{32} and R^{33} independently are hydrogen or C_{1-6}-alkyl, or

R^{32} and R^{33} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

R^{29}, R^{30} and R^{31} independently are

- hydrogen, halogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{34}$, $-NR^{34}R^{35}$, $-SR^{34}$, $-S(O)R^{34}$, $-S(O)_2R^{34}$, $-C(O)NR^{34}R^{35}$, $-OC(O)NR^{34}R^{35}$, $-NR^{34}C(O)R^{35}$, $-OCH_2C(O)NR^{34}R^{35}$, $-C(O)R^{34}$ or $-C(O)OR^{34}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

  which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{34}$, $-NR^{34}R^{35}$ and C_{1-6}-alkyl,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

  of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{34}$, $-NR^{34}R^{35}$ and C_{1-6}-alkyl,

  wherein R^{34} and R^{35} independently are hydrogen, C_{1-6}-alkyl or aryl,

  or R^{34} and R^{35} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{29}, R^{30} and R^{31} when attached to the same ring carbon atom or different ring carbon atoms together may form a radical $-O-(CH_2)_t-CR^{36}R^{37}-(CH_2)_l-O-$, $-(CH_2)_t-CR^{36}R^{37}-(CH_2)_l-$ or $-S-(CH_2)_t-CR^{36}R^{37}-(CH_2)_l-S-$,

wherein

t and l independently are 0, 1, 2, 3, 4 or 5,

R^{36} and R^{37} independently are hydrogen or C_{1-6}-alkyl,

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

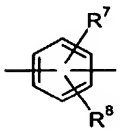
An embodiment of the invention provides compounds, wherein R^1, R^2, R^3, R^4 and R^5 are hydrogen.

An embodiment of the invention provides compounds, wherein A is –CHF-.

An embodiment of the invention provides compounds, wherein A is $-CH(OR^6)-$, wherein R^6 is as defined above.

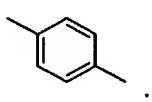
An embodiment of the invention provides compounds, wherein A is –CH(OH)-.

An embodiment of the invention provides compounds, wherein Z is



wherein R^7 and R^8 are as defined above.

An embodiment of the invention provides compounds, wherein Z is



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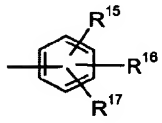
An embodiment of the invention provides compounds, wherein X is -C(O)NH-, $-C(O)NHCH_2-$, $-C(O)NHCH(CH_3)-$, $-C(O)CH_2-$ or -C(O)-.

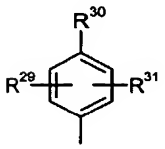
An embodiment of the invention provides compounds, wherein X is -C(O)NH-.

An embodiment of the invention provides compounds, wherein D is



wherein R^{15}, R^{16} and R^{17} independently are hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$ or C_{1-6}-alkoxy.

An embodiment of the invention provides compounds, wherein E is



wherein R^{29} and R^{31} are both hydrogen, and R^{30} is cyclohexenyl,

- which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{34}$, $-NR^{34}R^{35}$ and C_{1-6}-alkyl,

- wherein R^{34} and R^{35} independently are hydrogen, C_{1-6}-alkyl or aryl,

- or R^{34} and R^{35} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds.

-

An embodiment of the invention provides compounds, wherein R^{29}, R^{30} and R^{31} independently are hydrogen, C_{1-6}-alkyl, phenyl, C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl.

An embodiment of the invention provides compounds, wherein R^{29} and R^{31} are both hydrogen and R^{30} is C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl

In an embodiment the invention provides the compounds as below:

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(3-methoxy-5-trifluoromethylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[3-(3,5-Bis(trifluoromethyl)phenyl)-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[3-(3-Bromophenyl)-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(3-trifluoromethylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(3-fluoro-5-trifluoromethylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[3-(3-Cyano-5-trifluoromethylphenyl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[3-(3-Cyano-5-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[3-(3-Bromo-5-trifluoromethylphenyl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3-methoxy-5-trifluoromethylphenyl)ureidomethyl]-benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[3-(3-Bromophenyl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[3-(3-Bromo-5-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(S)-*Trans*-3-{4-[3-(3,5-Bis(trifluoromethyl)phenyl)-1-(4-*tert*-butylcyclohexyl)ureidomethyl]-benzoylamino}-2-hydroxypropionic acid

(R)-*Trans*-3-{4-[3-(3,5-bis(trifluoromethyl)phenyl)-1-(4-*tert*-butylcyclohexyl)ureidomethyl]-benzoylamino}-2-hydroxypropionic acid

Trans-(R)-3-{4-[3-(3-methyl-5-trifluoromethylphenyl)-1-(4-*tert*-butylcyclohexyl)ureidomethyl]-benzoylamino}-2-hydroxypropionic acid

(RS)-3-{4-[1-(4-*tert*-Butylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(RS)-3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(S)-3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[3-(3-Chlorophenyl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-phenylureidomethyl]benzoylamino}-2-hydroxy-propionic acid

(R)-3-{4-[3-Benzyl-1-(4-cyclohex-1-enylphenyl)ureidomethyl]benzoylamino}-2-hydroxy-propionic acid

(RS)-3-{4-[1-(4-Cyclohex-1-enylphenyl)3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2-fluoropropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]benzoyl-amino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexen-1-ylphenyl)-3-(3-methanesulfonyl-4-trifluoromethoxyphenyl)-ureidomethyl]benzoylamino}-2-hydroxypropionic acid

Trans-(R)-3-{4-[-3-(3,5-bis(methyl)phenyl)-1-(4-*tert*-butylcyclohexyl)ureidomethyl]benzoyl-amino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-(3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3-fluoro-5-trifluoromethylphenyl)ureidomethyl]-benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(3-methylsulfanylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(2,2,4,4-tetrafluoro-4*H*-benzo[1,3]dioxin-6-yl)ureido-methyl]benzoylamino}-2-hydroxypropionic acid

3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2(R)-methoxypropionic acid:

3-(4-{3-(3,5-Dichlorophenyl)-1-[4-(2-methylcyclohex-1-enyl)phenyl]ureidomethyl}benzoyl-amino)-2-(R)-hydroxypropionic acid and (R,S)-3-(4-{3-(3,5-dichlorophenyl)-1-[4-(6-methylcyclohex-1-enyl)phenyl]ureidomethyl}benzoylamino)-2-(R)-hydroxypropionic acid

3-{4-[1-[4-(4-*tert*-Butylcyclohex-1-enyl)phenyl]-3-(3,5-dichlorophenyl)ureidomethyl]benzoyl-amino}-2-(R)-hydroxypropionic acid

(R,S)-3-(4-(3-(3,5-dichlorophenyl)-1-(4-(3-methylcyclohex-1-enyl)phenyl)ureidomethyl)benzoylamino)-2-hydroxypropionic acid

3-{4-[3-[1(*S*)-(4-Chlorophenyl)ethyl]-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}-2(*R*)-hydroxypropionic acid

3-{4-[3-Biphenyl-2-ylmethyl-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}-2(*R*)-hydroxypropionic acid

(R)-3-{4-[3-(4-Cyano-3-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[3-(3-*tert*-Butylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(3-hydroxymethyl-4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-*tert*-Butylphenyl)-3-(3,4-dichlorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,4-dichlorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(3,4-dichlorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(2,2,4,4-tetrafluoro-4*H*-benzo[1,3]dioxin-6-yl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-*tert*-Butylphenyl)-3-(2,2,4,4-tetrafluoro-4*H*-benzo[1,3]dioxin-6-yl)ureidomethyl]-benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(2,2,4,4-tetrafluoro-4*H*-benzo[1,3]dioxin-6-yl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-*tert*-Butylphenyl)-3-(3,4-difluorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(3,4-difluorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,4-difluorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(4-fluoro-3-nitrophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(4-isopropylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,4-dichlorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[3-(4-Acetylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}-2-hydroxy-propionic acid

3-{4-[3-[1(RS)-(4-Bromophenyl)ethyl]-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}-2(R)-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(3,5-difluorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-[4-({(4-*tert*-Butylcyclohexyl)-[2-(4-trifluoromethoxyphenyl)acetyl]amino}methyl)benzoyl-amino]-2-hydroxypropionic acid

(R)-3-[4-({(4-*tert*-Butylcyclohexyl)-[2-(3-fluoro-5-trifluoromethylphenyl)acetyl]amino}methyl)-benzoylamino]-2-hydroxypropionic acid

(R)-3-[4-({(2,2-Diphenylethyl)-[2-(3-fluoro-5-trifluoromethylphenyl)acetyl]amino}methyl)-benzoylamino]-2-hydroxypropionic acid

(R)-3-(4-{[(5-Chlorobenzo[*b*]thiophene-3-carbonyl)-(2,2-diphenylethyl)amino]methyl}benzoyl-amino)-2-hydroxypropionic acid

(R)-3-[4-({(2,2-Diphenylethyl)-[2-(4-trifluoromethoxyphenyl)acetyl]amino}methyl)benzoyl-amino]-2-hydroxypropionic acid

(R)-3-(4-{[(4-*tert*-Butylcyclohexyl)-(5-chlorobenzo[*b*]thiophene-3-carbonyl)amino]methyl}-benzoylamino)-2-hydroxypropionic acid

(R)-3-(4-{[(2,2-Diphenylethyl)-(5-trifluoromethoxy-1*H*-indole-2-carbonyl)amino]methyl}-benzoylamino)-2-hydroxypropionic acid

(R)-3-[4-({(4-Cyclohexylphenyl)-[(4-trifluoromethoxyphenyl)acetyl]amino}methyl)benzoyl-amino]-2-hydroxypropionic acid

(R)-3-[4-({(4-Cyclohexylphenyl)-[(3-trifluoromethoxyphenyl)acetyl]amino}methyl)benzoyl-amino]-2-hydroxypropionic acid

(R)-3-[4-({(4-Cyclohexylphenyl)-[(3-fluoro-5-trifluoromethylphenyl)acetyl]amino}methyl)-benzoylamino]-2-hydroxypropionic acid

(R)-3-(4-{([(3,5-Bis(trifluoromethyl)phenyl)acetyl]-(4-cyclohexylphenyl)amino)methyl}benzoyl-amino)-2-hydroxypropionic acid

(R)-3-[4-({(4-Cyclohexylphenyl)-[(3-trifluoromethylphenyl)acetyl]amino}methyl)benzoylamino]-2-hydroxypropionic acid

(R)-3-[4-({(4-Cyclohexylphenyl)-[(3,4-dichlorophenyl)acetyl]amino}methyl)benzoylamino]-2-hydroxypropionic acid

(R)-3-(4-{[[(3-Bromophenyl)acetyl]-(4-cyclohexylphenyl)amino]methyl}benzoylamino)-2-hydroxypropionic acid

(R)-3-(4-{[(Biphenyl-4-ylacetyl)-(4-cyclohexylphenyl)amino]methyl}benzoylamino)-2-hydroxy-propionic acid

(R)-3-(4-{[(4-Cyclohexylphenyl)-(2-naphthylacetyl)amino]methyl}benzoylamino)-2-hydroxy-propionic acid

(R)-3-(4-{[(3-(3,5-Bis(trifluoromethyl)phenyl)propionyl)-(4-cyclohexylphenyl)amino]methyl}-benzoylamino)-2-hydroxypropionic acid

(R)-3-[4-({(4-Cyclohexylphenyl)-[3-(3-nitrophenyl)propionyl]amino}methyl)benzoylamino]-2-hydroxypropionic acid

(2R)-N-[4-({4-cyclohexyl[(3,5-dichloroanilino)carbonyl]anilino}methyl)benzoyl]-2-hydroxy-β-alanine (2R)-N-[4-({[1,1'-biphenyl]-4-yl[(3,5-dichloroanilino)carbonyl]amino}methyl)benzoyl]-2-hydroxy-β-alanineIn an embodiment the invention provides the compound (R)-[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2R-hydroxypropionic acid as a tert-butylamine salt.

In an embodiment the invention provides the compound (R)-[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2R-hydroxypropionic acid as an L-arginine salt.

In an embodiment the invention provides the compound (R)-[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2R-hydroxypropionic acid as a salt with N,N'-dibenzylethylenediamine.

In an embodiment the invention provides the compound (R)-[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2R-hydroxypropionic acid as a salt with N,N'-dibenzylethylenediamine as a 2:1 ratio between compound and N,N'-dibenzylethylenediamine.

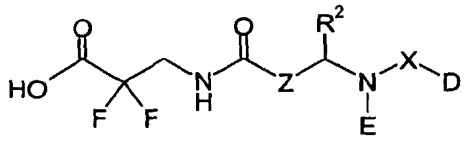
In an embodiment the invention provides the compound (2R)-N-[4-({[1,1'-biphenyl]-4-yl[(3,5-dichloroanilino)carbonyl]amino}methyl)benzoyl]-2-hydroxy-β-alanine and benzathine.

In an embodiment the invention provides the compound (2R)-N-[4-({[1,1'-biphenyl]-4-yl[(3,5-dichloroanilino)carbonyl]amino}methyl)benzoyl]-2-hydroxy-β-alanine and benzathine as a 2:1 ratio between compound and N,N'-dibenzylethylenediamine.

In an embodiment the invention provides the compound ((2R)-N-[4-({4-cyclohexyl[(3,5-dichloroanilino)carbonyl]anilino}methyl)benzoyl]-2-hydroxy-β-alanine as a salt with N,N'-dibenzylethylenediamine.

In an embodiment the invention provides the compound ((2R)-N-[4-({4-cyclohexyl[(3,5-dichloroanilino)carbonyl]anilino}methyl)benzoyl]-2-hydroxy-β-alanine as a salt with N,N'-dibenzylethylenediamine in a 2:1 ratio of compound to N,N'-dibenzylethylenediamine.

In an embodiment the invention provides a glucagon antagonist represented by the general formula (I):



(I)

wherein

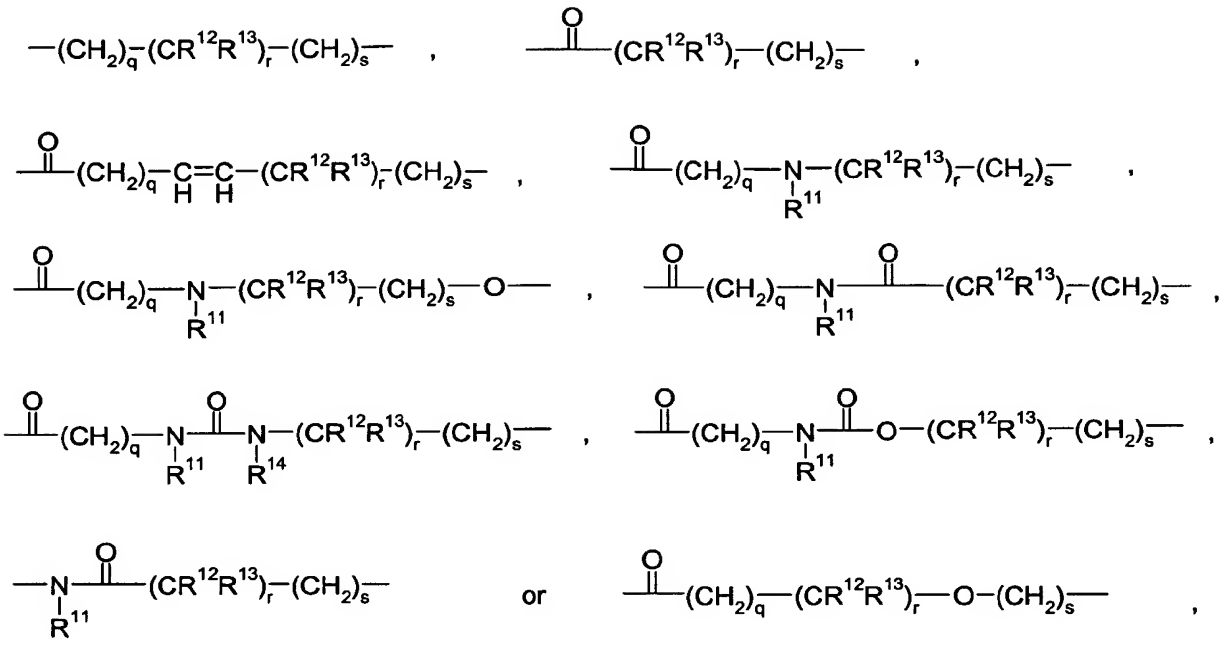
R^2 is hydrogen or C_{1-6}-alkyl,

Z is arylene or a divalent radical derived from a 5 or 6 membered heteroaromatic ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur,

which may optionally be substituted with one or two groups R^7 and R^8 selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^9$, $-NR^9R^{10}$ and C_{1-6}-alkyl,

wherein R^9 and R^{10} independently are hydrogen or C_{1-6}-alkyl,

X is



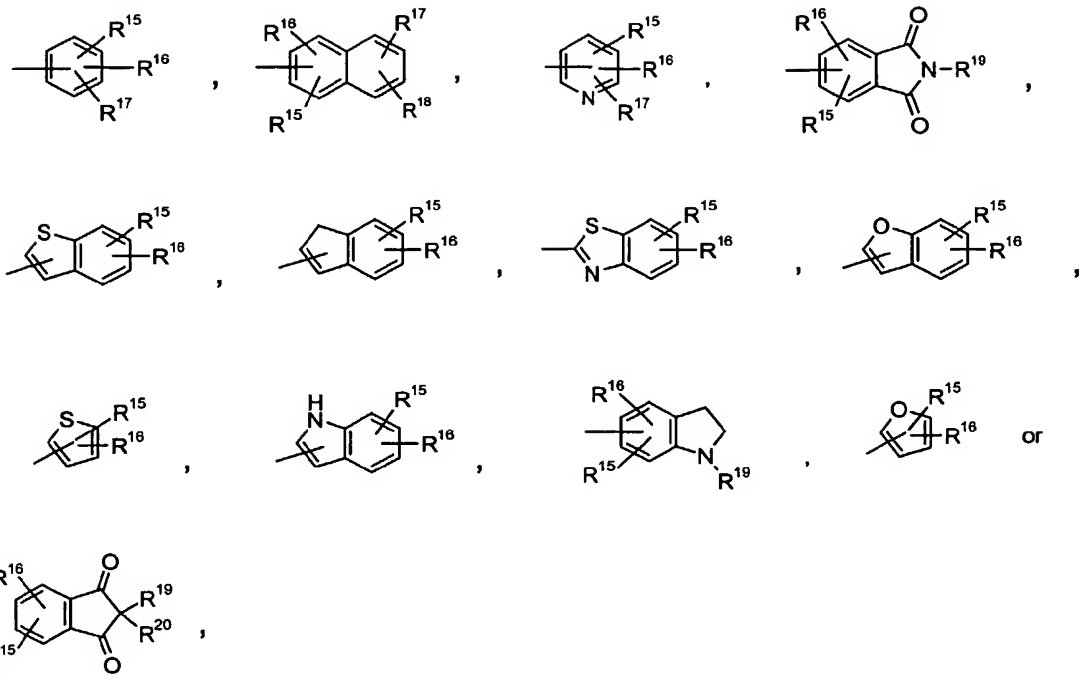
wherein

r is 0 or 1,

q and s independently are 0, 1, 2 or 3,

R^{11}, R^{12}, R^{13} and R^{14} independently are hydrogen or C_{1-6}-alkyl,

D is



wherein

R^{15}, R^{16}, R^{17} and R^{18} independently are

- hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{21}$, $-NR^{21}R^{22}$, $-SR^{21}$, $-NR^{21}S(O)_2R^{22}$, $-S(O)_2NR^{21}R^{22}$, $-S(O)NR^{21}R^{22}$, $-S(O)R^{21}$, $-S(O)_2R^{21}$, $-C(O)NR^{21}R^{22}$, $-OC(O)NR^{21}R^{22}$, $-NR^{21}C(O)R^{22}$, $-CH_2C(O)NR^{21}R^{22}$, $-OCH_2C(O)NR^{21}R^{22}$, $-CH_2OR^{21}$, $-CH_2NR^{21}R^{22}$, $-OC(O)R^{21}$, $-C(O)R^{21}$ or $-C(O)OR^{21}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

  which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{21}$, $-NR^{21}R^{22}$ and C_{1-6}-alkyl,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkoxy, C_{3-8}-cycloalkyloxy, C_{3-8}-cycloalkyl-C_{1-6}-alkylthio, C_{3-8}-cycloalkylthio,

C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{21}$, $-NR^{21}R^{22}$ and C_{1-6}-alkyl,

wherein R^{21} and R^{22} independently are hydrogen, C_{1-6}-alkyl or aryl,

or R^{21} and R^{22} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{15} to R^{18} when placed in adjacent positions together may form a bridge $-(CR^{23}R^{24})_a-O-(CR^{25}R^{26})_c-O-$,

wherein

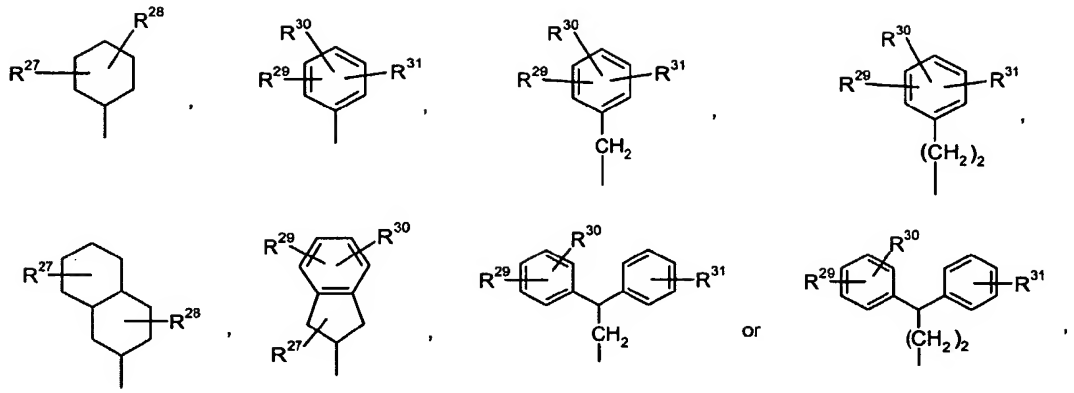
a is 0, 1 or 2,

c is 1 or 2,

R^{23}, R^{24}, R^{25} and R^{26} independently are hydrogen, C_{1-6}-alkyl or fluorine,

R^{19} and R^{20} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,

E is



wherein

R^{27} and R^{28} independently are

hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{32}$, $-NR^{32}R^{33}$, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl or aryl,

wherein the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{32}$, $-NR^{32}R^{33}$ and C_{1-6}-alkyl,

wherein

R^{32} and R^{33} independently are hydrogen or C_{1-6}-alkyl, or

R^{32} and R^{33} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

R^{29}, R^{30} and R^{31} independently are

- hydrogen, halogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{34}$, $-NR^{34}R^{35}$, $-SR^{34}$, $-S(O)R^{34}$, $-S(O)_2R^{34}$, $-C(O)NR^{34}R^{35}$, $-OC(O)NR^{34}R^{35}$, $-NR^{34}C(O)R^{35}$, $-OCH_2C(O)NR^{34}R^{35}$, $-C(O)R^{34}$ or $-C(O)OR^{34}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

  which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{34}$, $-NR^{34}R^{35}$ and C_{1-6}-alkyl,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

  of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{34}$, $-NR^{34}R^{35}$ and C_{1-6}-alkyl,

  wherein R^{34} and R^{35} independently are hydrogen, C_{1-6}-alkyl or aryl,

  or R^{34} and R^{35} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{29}, R^{30} and R^{31} when attached to the same ring carbon atom or different ring carbon atoms together may form a radical $-O-(CH_2)_t-CR^{36}R^{37}-(CH_2)_l-O-$, $-(CH_2)_t-CR^{36}R^{37}-(CH_2)_l-$ or $-S-(CH_2)_t-CR^{36}R^{37}-(CH_2)_l-S-$,

wherein

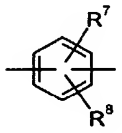
t and l independently are 0, 1, 2, 3, 4 or 5,

R^{36} and R^{37} independently are hydrogen or C_{1-6}-alkyl,

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these.

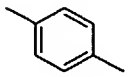
In an embodiment the invention provides a compound, wherein R^2 is hydrogen.

In an embodiment the invention provides a compound, wherein Z is

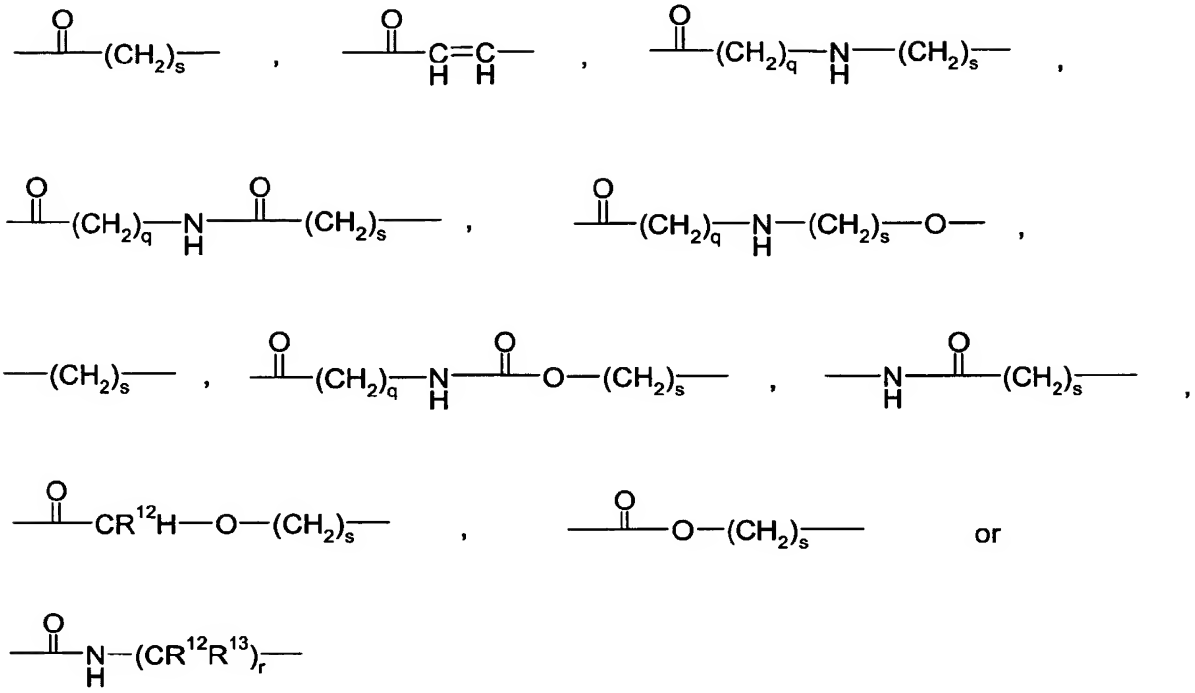


wherein R^7 and R^8 are as defined as above.

In an embodiment the invention provides a compound, wherein Z is

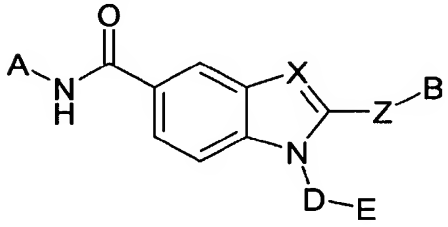


In an embodiment the invention provides a compound, wherein X is



wherein q is 0 or 1, r is 0 or 1, s is 0, 1 or 2, and R^{12} and R^{13} independently are hydrogen or C_{1-6}-alkyl.

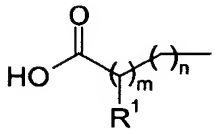
In an embodiment the invention provides a glucagon antagonist as represented by the general formula (I):



(I)

wherein

A is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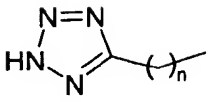

,

m is 0 or 1,

n is 0, 1, 2 or 3,

with the proviso that m and n must not both be 0,

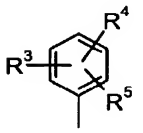
R^1 is hydrogen, fluoro or $-(CH_2)_o-OR^2$,

o is 0 or 1,

R^2 is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkanoyl, aryl or aryl-C_{1-6}-alkyl,

X is –N= or –CH=,

B is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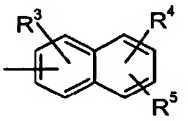
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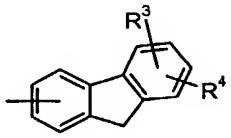
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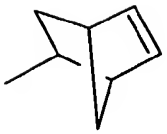


V and W independently are –CH= or –N=,

Y is –O-, –S- or –NH-,

R^3, R^4 and R^5 independently are

- hydrogen, halogen, -CN, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^6$, $-NR^6R^7$, $-SR^6$, $-NR^6S(O)_2R^7$, $-S(O)_2NR^6R^7$, $-S(O)NR^6R^7$, $-S(O)R^6$, $-S(O)_2R^6$, $-C(O)NR^6R^7$, $-OC(O)NR^6R^7$, $-NR^6C(O)R^7$,

$-CH_2C(O)NR^6R^7$, $-OCH_2C(O)NR^6R^7$, $-OCH_2C(O)OR^6$, $-OC(O)R^6$, $-C(O)R^6$ or $-C(O)OR^6$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from fluoro, -CN, $-CF_3$, $-OCF_3$, $-OR^6$ and $-NR^6R^7$,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkoxy, C_{3-8}-cycloalkyloxy, C_{3-8}-cycloalkyl-C_{1-6}-alkylthio, C_{3-8}-cycloalkylthio, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl,

of which the cyclic moieties may optionally be substituted with one or more substituents selected from fluoro, $-C(O)OR^6$, -CN, $-CF_3$, $-OCF_3$, $-OR^7$, $-NR^6R^7$ and C_{1-6}-alkyl,

- aryl, arylthio, aryl-C_{1-6}-alkylthio, aryloxy, aryloxycarbonyl, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

of which the cyclic moieties may optionally be substituted with one or more substituents selected from halogen, $-C(O)OR^6$, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^7$, $-NR^6R^7$ and C_{1-6}-alkyl,

R^6 and R^7 independently are hydrogen or C_{1-6}-alkyl,

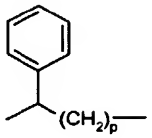
or R^6 and R^7 when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^3 to R^5 when placed in adjacent positions together may form a bridge $-(CR^8R^9)_s-O-(CR^{10}R^{11})_t-O-$,

s is 0, 1 or 2,

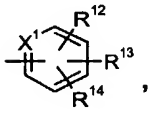
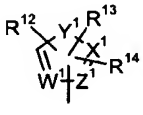
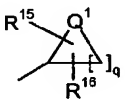
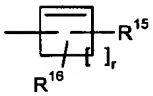
t is 1 or 2,

R^8, R^9, R^{10} and R^{11} independently are hydrogen, C_{1-6}-alkyl or fluoro,

D is $-(CH_2)_p-$,  or $-(CH_2)_p-O-$,

p is 0, 1, 2, 3 or 4,

E is

 ,  ,  or 

X^1, Z^1 and W^1 independently are –CH= or –N=,

Y^1 is –O-, –S- or –NH-,

Q^1 is $-CH_2-$ or –NH-,

q is 2, 3, 4, 5 or 6,

r is 1, 2, 3, 4 or 5,

R^{12}, R^{13} and R^{14} independently are

- hydrogen, halogen, -CN, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{17}$, $-NR^{17}R^{18}$, $-SR^{17}$, $-NR^{17}S(O)_2R^{18}$, $-S(O)_2NR^{17}R^{18}$, $-S(O)NR^{17}R^{18}$, $-S(O)R^{17}$, $-S(O)_2R^{17}$, $-C(O)NR^{17}R^{18}$, $-OC(O)NR^{17}R^{18}$, $-NR^{17}C(O)R^{18}$, $-CH_2C(O)NR^{17}R^{18}$, $-OCH_2C(O)NR^{17}R^{18}$, $-OC(O)R^{17}$, $-C(O)R^{17}$ or $-C(O)OR^{17}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from fluoro, -CN, $-CF_3$, $-OCF_3$, $-OR^{17}$ and $-NR^{17}R^{18}$,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkoxy, C_{3-8}-cycloalkyloxy, C_{3-8}-cycloalkyl-C_{1-6}-alkylthio, C_{3-8}-cycloalkylthio, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl,

  of which the cyclic moieties may optionally be substituted with one or more substituents selected from fluoro, $-C(O)OR^{17}$, -CN, $-CF_3$, $-OCF_3$, $-OR^{17}$ and $-NR^{17}R^{18}$,

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

  of which the cyclic moieties may optionally be substituted with one or more substituents selected from halogen, $-C(O)OR^{17}$, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{17}$, $-NR^{17}R^{18}$ and C_{1-6}-alkyl,

R^{17} and R^{18} independently are hydrogen or C_{1-6}-alkyl,

or R^{17} and R^{18} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{12} to R^{14} when placed in adjacent positions together may form a bridge $-(CR^{19}R^{20})_x-O-(CR^{21}R^{22})_y-O-$,

x is 0, 1 or 2,

y is 1 or 2,

R^{19}, R^{20}, R^{21} and R^{22} independently are hydrogen, C_{1-6}-alkyl or fluoro,

R^{15} and R^{16} independently are hydrogen, halogen, -CN, $-CF_3$, $-OR^{23}$, $-NR^{23}R^{24}$, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, aryl or aryl-C_{1-6}-alkyl,

wherein the cyclic moieties may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{23}$, $-NR^{23}R^{24}$ and C_{1-6}-alkyl,

R^{23} and R^{24} independently are hydrogen or C_{1-6}-alkyl, or

R^{23} and R^{24} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or E is

C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{25}$,$-SR^{25}$, $-NR^{25}R^{26}$ and C_{1-6}-alkyl,

R^{25} and R^{26} independently are hydrogen or C_{1-6}-alkyl, or

R^{25} and R^{26} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

Z is $-(CR^{27}R^{28})_v-(O)_w-(CR^{29}R^{30})_z-$,

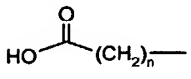
v and z independently are 0, 1 or 2,

w is 0 or 1,

R^{27}, R^{28}, R^{29} and R^{30} independently are hydrogen or C_{1-6}-alkyl,

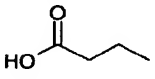
as well as any diastereomer or enantiomer or tautomeric form thereof including mixtures of these.

In an embodiment the invention provides a compound, wherein A is



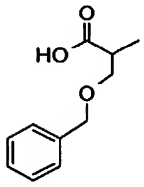
, wherein n is as defined above.

In an embodiment the invention provides a compound,wherein A is



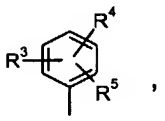
.

In an embodiment the invention provides a compound, wherein A is



.

In an embodiment the invention provides a compound, wherein B is



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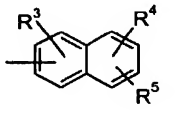

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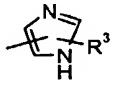

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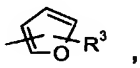

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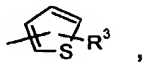

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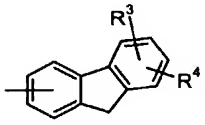
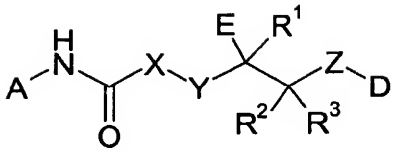


or

wherein R^3 to R^5 are as defined above.

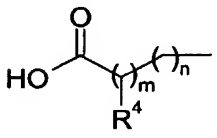
In an embodiment the invention provides a glucagon antagonist as represented by the general formula (I):



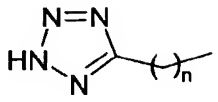
(I)

wherein

A is



or



,

m is 0 or 1,

n is 0, 1, 2 or 3,

with the proviso that m and n must not both be 0,

R^4 is hydrogen, halogen or $-(CH_2)_o-OR^5$,

o is 0 or 1,

R^5 is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkanoyl, aryl or aryl-C_{1-6}-alkyl,

R^1 and R^2 independently are hydrogen, halogen or C_{1-6}-alkyl, or R^1 and R^2 are combined to form a double bond,

R^3 is hydrogen, C_{1-6}-alkyl or halogen, or R^3 and R^2 are combined to form a double bond to oxygen,

X is arylene or heteroarylene, which may optionally be substituted with one or two groups R^6 and R^7 selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-NO_2$, $-OR^8$, $-NR^8R^9$ and C_{1-6}-alkyl,

R^8 and R^9 independently are hydrogen or C_{1-6}-alkyl,

Y is -C(O)-, -O-, -NR^{10}-, -S-, -S(O)-, -$S(O)_2$- or -$CR^{11}R^{12}$-,

R^{10} is hydrogen or C_{1-6}-alkyl,

R^{11} and R^{12} independently are hydrogen, C_{1-6}-alkyl or hydroxy, or R^{11} is combined with R^1 to form a double bond, and R^{12} is hydrogen, C_{1-6}-alkyl or hydroxy,

Z is -C(O)-$(CR^{13}R^{14})_p$-, -O-$(CR^{13}R^{14})_p$-, -S-$(CR^{13}R^{14})_p$-, –S(O)-$(CR^{13}R^{14})_p$-, -$S(O)_2$-$(CR^{13}R^{14})_p$-, -NR^{15}-$(CR^{13}R^{14})_p$- or -$(CR^{13}R^{14})_p$-,

p is 0, 1 or 2,

R^{13} and R^{14} independently are selected from hydrogen, -CF_3, -OCF_3, -$OCHF_2$ and C_{1-6}-alkyl,

R^{15} is hydrogen or C_{1-6}-alkyl,

D is aryl or heteroaryl, which may optionally be substituted with one or more substituents R^{16}, R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, wherein

R^{16}, R^{17}, R^{18} and R^{19} independently are

- hydrogen, halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$S(O)_2CF_3$, -SCF_3, -NO_2, -OR^{22}, -$NR^{22}R^{23}$, -SR^{22}, -$NR^{22}S(O)_2R^{23}$, -$S(O)_2NR^{22}R^{23}$, -$S(O)NR^{22}R^{23}$, -$S(O)R^{22}$, -$S(O)_2R^{22}$, -$C(O)NR^{22}R^{23}$, -$OC(O)NR^{22}R^{23}$, -$NR^{22}C(O)R^{23}$, -$CH_2C(O)NR^{22}R^{23}$, -$OCH_2C(O)NR^{22}R^{23}$, -CH_2OR^{22}, -$CH_2NR^{22}R^{23}$, -$OC(O)R^{22}$, -$C(O)R^{22}$ or -$C(O)OR^{22}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from halogen, -CN, -CF_3, -$OCHF_2$, -OCF_3, -NO_2, -OR^{22}, -$NR^{22}R^{23}$ and C_{1-6}-alkyl,

• C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkoxy, C_{3-8}-cycloalkyloxy, C_{3-8}-cycloalkyl-C_{1-6}-alkylthio, C_{3-8}-cycloalkylthio, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

of which the aromatic and non-aromatic ring systems optionally may be substituted with one or more substituents selected from halogen, $-C(O)OR^{22}$, -CN, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-NO_2$, $-OR^{22}$, $-NR^{22}R^{23}$ and C_{1-6}-alkyl,

R^{22} and R^{23} independently are hydrogen, C_{1-6}-alkyl, aryl-C_{1-6}-alkyl or aryl, or R^{22} and R^{23} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{16} to R^{19} when placed in adjacent positions together may form a bridge $-(CR^{24}R^{25})_a-O-(CR^{26}R^{27})_c-O-$,

a is 0, 1 or 2,

c is 1 or 2,

R^{24}, R^{25}, R^{26} and R^{27} independently are hydrogen, C_{1-6}-alkyl or fluoro,

R^{20} and R^{21} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,

E is

C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl, which may optionally be substituted with one or two substituents R^{28} and R^{29}, which are independently selected from

• hydrogen, halogen, -CN, -CF_3, -OCF_3, -$OCHF_2$, -OR^{33}, -$NR^{33}R^{34}$, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heteroaryl and aryl,

wherein the heteroaryl and aryl groups optionally may be substituted with one or more substituents selected from halogen, -CN, -CF_3, -OCF_3, -$OCHF_2$, -NO_2, -OR^{33}, -$NR^{33}R^{34}$ and C_{1-6}-alkyl,

R^{33} and R^{34} independently are hydrogen or C_{1-6}-alkyl,

or R^{33} and R^{34} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

aryl, heteroaryl, aryl-C_{2-6}-alkenyl or aryl-C_{2-6}-alkynyl, of which the aryl and heteroaryl moieties may optionally be substituted with one or more substitutents R^{28}, R^{29}, R^{30}, R^{31} and R^{32},

wherein R^{28} and R^{29} are as defined above, and R^{30}, R^{31} and R^{32} are independently selected from

• hydrogen, halogen, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -SCF_3, -OR^{35}, -$NR^{35}R^{36}$, -SR^{35}, -$S(O)R^{35}$, -$S(O)_2R^{35}$, -$C(O)NR^{35}R^{36}$, -$OC(O)NR^{35}R^{36}$, -$NR^{35}C(O)R^{36}$, -$OCH_2C(O)NR^{35}R^{36}$, -$C(O)R^{35}$ and -$C(O)OR^{35}$,

• C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from halogen, -CN, -CF_3, -OCF_3, -$OCHF_2$, -NO_2, -OR^{35}, -$NR^{35}R^{36}$ and C_{1-6}-alkyl,

• C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl and heteroaryl-C_{2-6}-alkynyl,

of which the aromatic and non-aromatic ring systems optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,

wherein R^{35} and R^{36} independently are hydrogen, C_{1-6}-alkyl or aryl,

or R^{35} and R^{36} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

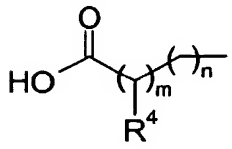
or two of the substituents R^{30}, R^{31} and R^{32} when attached to the same ring carbon atom or adjacent ring carbon atoms together may form a bridge $-O-(CH_2)_t-CR^{37}R^{38}-(CH_2)_l-O-$, $-(CH_2)_t-CR^{37}R^{38}-(CH_2)_l-$ or $-S-(CH_2)_t-CR^{37}R^{38}-(CH_2)_l-S-$,

t and l independently are 0, 1, 2, 3, 4 or 5,

R^{37} and R^{38} independently are hydrogen or C_{1-6}-alkyl,

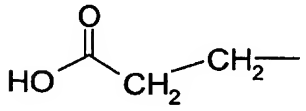
as well as any diastereomer or enantiomer or tautomeric form thereof including mixtures of these.

In an embodiment the invention provides compounds, wherein A is

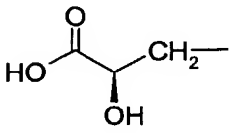


wherein m, n and R^4 are as defined above.

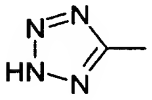
In an embodiment the invention provides compounds, wherein A is



In an embodiment the invention provides compounds, wherein A is

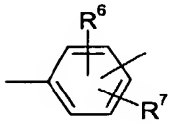


In an embodiment the invention provides compounds, wherein A is



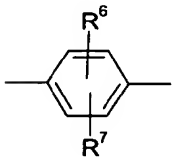
In an embodiment the invention provides compounds, wherein X is monocyclic arylene or heteroarylene, which may optionally be substituted as defined above.

In an embodiment the invention provides compounds, wherein X is



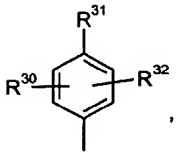
wherein R^6 and R^7 are as defined above.

In an embodiment the invention provides compounds, wherein X is



wherein R^6 and R^7 are as defined above.

In an embodiment the invention provides compounds, wherein E is



wherein R^{30}, R^{31} and R^{32} are as defined above.

In an embodiment the invention provides compounds, wherein R^{30}, R^{31} and R^{32} independently are

- hydrogen,

- halogen, $-OCF_3$, $-OCHF_2$ or $-SCF_3$,

- C_{1-6}-alkyl, which may optionally be substituted with one or more substituents selected from fluoro, -CN, $-CF_3$, $-OCF_3$, $-OR^{35}$ and $-NR^{35}R^{36}$,

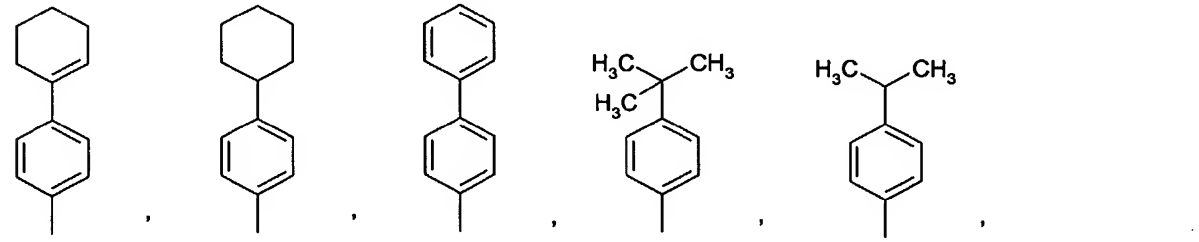
- cyclohexyl or cyclohex-1-enyl, which may optionally be substituted with one or more substituents selected from fluoro, -CN, $-CF_3$, $-OCF_3$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,

- phenyl which may optionally be substituted with one or more substitutents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,

- phenoxy or benzyloxy, of which the phenyl moieties may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,

R^{35} and R^{36} independently are hydrogen or C_{1-6}-alkyl.

In an embodiment the invention provides compounds, wherein E is



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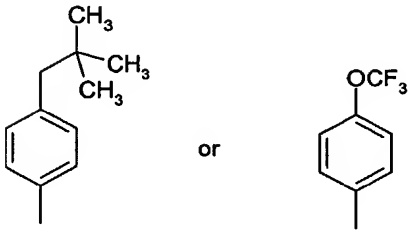


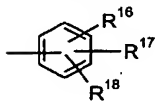
In an embodiment the invention provides compounds, wherein R^1 and R^2 are both hydrogen.

In an embodiment the invention provides compounds, wherein R^1 and R^2 are combined to form a double bond.

In an embodiment the invention provides compounds, wherein R^3 is hydrogen.

In an embodiment the invention provides compounds, wherein Z is NH or -C(O)-.

In an embodiment the invention provides compounds, wherein D is



wherein R^{16}, R^{17} and R^{18} are as defined above.

In an embodiment the invention provides compounds, wherein R^{16}, R^{17} and R^{18} independently are

- hydrogen, halogen, $-CF_3$, $-OCF_3$, $-SCF_3$, C_{1-6}-alkyl, C_{1-6}-alkoxy, phenyl, cyclopentyl, cyclohexyl or phenoxy,

- or two of the groups R^{16} to R^{18} when placed in adjacent positions together may form a bridge $-O-(CF_2)_2-O-$, $-CF_2-O-CF_2-O-$ or $-O-CH_2-O-$.

In an embodiment the invention provides compounds such as

(Z)-3-{4-[4-Biphenyl-4-yl-2-(4-cyclohexylphenyl)-4-oxobut-2-enoyl]benzoylamino}propionic acid

(Z)-3-{4-[2-Biphenyl-4-yl-4-(4-chlorophenyl)-4-oxobut-2-enoyl]benzoylamino}propionic acid

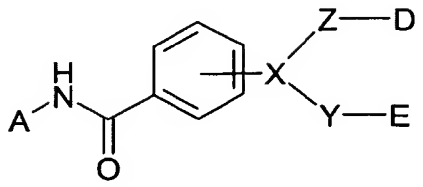
(Z)-3-{4-[4-(4-tert-Butylphenyl)-4-oxo-2-(4-trifluoromethoxyphenyl)but-2-enoyl]benzoylamino}-propionic acid

3-{4-[4-(3,5-Bis-trifluoromethylphenyl)-2-(4-cyclohexylphenyl)-4-oxo-butyryl]benzoylamino}-propionic acid

((R)3-{4-[4-(3,5-Bis-trifluoromethylphenyl)-2-(4-cyclohexylphenyl)-4-oxo-butyryl]benzoylamino}-propionic acid

(S)3-{4-[4-(3,5-Bis-trifluoromethylphenyl)-2-(4-cyclohexylphenyl)-4-oxo-butyryl]benzoylamino}-propionic acid

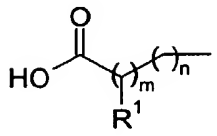
In an embodiment the invention provides glucagon antagonists as represented by the general formula (I):



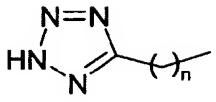
(I)

wherein

A is



or



,

m is 0 or 1,

n is 0, 1, 2 or 3,

with the proviso that m and n must not both be 0,

R^1 is hydrogen, fluoro or $-(CH_2)_o-OR^2$,

o is 0 or 1,

R^2 is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkanoyl, aryl or aryl-C_{1-6}-alkyl,

X is N, CH or C with a double bond to one substituent,

Z is $-CR^3R^4-$, $-(C=O)-(NR^5)-(C_{1-6}\text{-alkyl})_K-$, $-(C=O)-O-(C_{1-6}\text{-alkyl})_K-$, $-(C=O)-(C_{1-6}\text{-alkyl})_K-$, $-(C_{1-6}\text{-alkyl})_K(C=O)-O-$, $-(C=O)-O-(C_{2-6}\text{-alkenyl})_K-$, $-(C=O)-(C_{2-6}\text{-alkenyl})_K-$, $-(C_{1-6}\text{-alkenyl})_K(C=O)-O-$

wherein k is 0 or 1,

R^3, R^4 and R^5 are independently selected from hydrogen, C_{1-6}-alkyl or aryl,

Y is $-(C_{1-6}\text{-alkyl})_s\text{-}(C{=}O)\text{-}(C_{1-6}\text{-alkyl})_t\text{-}$, $-(C_{1-6}\text{-alkenyl})_s\text{-}(C{=}O)\text{-}(C_{1-6}\text{-alkyl})_t\text{-}$, $-C_{1-6}\text{-alkyl-}$, $\text{-}C_{2-6}\text{-alkenyl-}$, or $\text{-}CR^6R^7\text{-}$

wherein s and t independently are 0 or 1;

wherein R^6, R^7 and R^8 independently are selected from hydrogen, C_{1-6}-alkyl and aryl;

D is aryl or heteroaryl, which may optionally be substituted with one or more substituents R^{16}, R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, wherein

R^{16}, R^{17}, R^{18} and R^{19} independently are

- hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{22}$, $-NR^{22}R^{23}$, $-SR^{22}$, $-NR^{22}S(O)_2R^{23}$, $-S(O)_2NR^{22}R^{23}$, $-S(O)NR^{22}R^{23}$, $-S(O)R^{22}$, $-S(O)_2R^{22}$, $-C(O)NR^{22}R^{23}$, $-OC(O)NR^{22}R^{23}$, $-NR^{22}C(O)R^{23}$, $-CH_2C(O)NR^{22}R^{23}$, $-OCH_2C(O)NR^{22}R^{23}$, $-CH_2OR^{22}$, $-CH_2NR^{22}R^{23}$, $-OC(O)R^{22}$, $-C(O)R^{22}$ or $-C(O)OR^{22}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

  which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{22}$, $-NR^{22}R^{23}$ and C_{1-6}-alkyl,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkoxy, C_{3-8}-cycloalkyloxy, C_{3-8}-cycloalkyl-C_{1-6}-alkylthio, C_{3-8}-cycloalkylthio, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

  of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, $-C(O)OR^{22}$, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{22}$, $-NR^{22}R^{23}$ and C_{1-6}-alkyl,

R^{22} and R^{23} independently are hydrogen, C_{1-6}-alkyl, aryl-C_{1-6}-alkyl or aryl, or R^{22} and R^{23} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{16} to R^{19} when placed in adjacent positions together may form a bridge $-(CR^{24}R^{25})_a-O-(CR^{26}R^{27})_c-O-$,

a is 0, 1 or 2,

c is 1 or 2,

R^{24}, R^{25}, R^{26} and R^{27} independently are hydrogen, C_{1-6}-alkyl or fluoro,

R^{20} and R^{21} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,

E is

C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl, which may optionally be substituted with one or two substituents R^{28} and R^{29}, which are independently selected from

- hydrogen, halogen, -CN, $-CF_3$, $-OR^{33}$, $-NR^{33}R^{34}$, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heteroaryl and aryl,

wherein the heteroaryl and aryl groups optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{33}$, $-NR^{33}R^{34}$ and C_{1-6}-alkyl,

R^{33} and R^{34} independently are hydrogen or C_{1-6}-alkyl,

or R^{33} and R^{34} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

aryl, heteroaryl, aryl-C_{2-6}-alkenyl or aryl-C_{2-6}-alkynyl, of which the cyclic moieties may optionally be substituted with one to three substitutents R^{30}, R^{31} and R^{32}, which are independently selected from

- hydrogen, halogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{35}$, $-NR^{35}R^{36}$, $-SR^{35}$, $-S(O)R^{35}$, $-S(O)_2R^{35}$, $-C(O)NR^{35}R^{36}$, $-OC(O)NR^{35}R^{36}$, $-NR^{35}C(O)R^{36}$, $-OCH_2C(O)NR^{35}R^{36}$, $-C(O)R^{35}$ and $-C(O)OR^{35}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-SCF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl and heteroaryl-C_{2-6}-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-SCF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,

wherein R^{35} and R^{36} independently are hydrogen, C_{1-6}-alkyl or aryl,

or R^{35} and R^{36} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

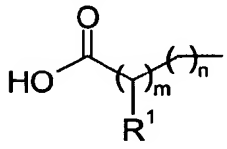
or two of the substituents R^{30}, R^{31} and R^{32} when attached to the same ring carbon atom or different ring carbon atoms together may form a radical $-O-(CH_2)_t-CR^{37}R^{38}-(CH_2)_l-O-$, $-(CH_2)_t-CR^{37}R^{38}-(CH_2)_l-$ or $-S-(CH_2)_t-CR^{37}R^{38}-(CH_2)_l-S-$,

t and l independently are 0, 1, 2, 3, 4 or 5,

R^{37} and R^{38} independently are hydrogen or C_{1-6}-alkyl,

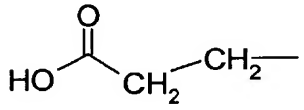
as well as any diastereomer or enantiomer or tautomeric form thereof including mixtures of these.

In an embodiment the invention provides compounds, wherein A is

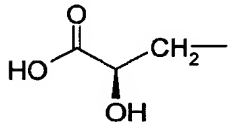


wherein m, n and R^4 are as defined above.

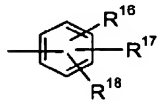
In an embodiment the invention provides compounds, wherein A is



In an embodiment the invention provides compounds, wherein A is



In an embodiment the invention provides compounds, wherein D is

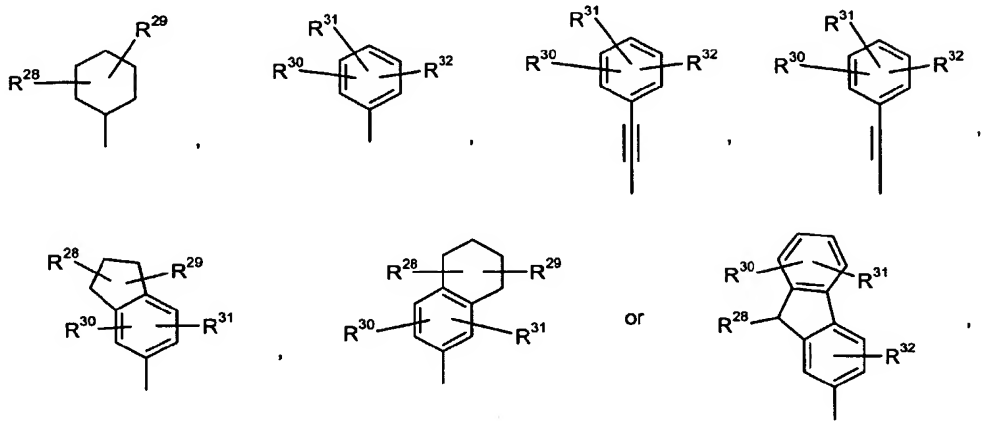


wherein R^{16}, R^{17} and R^{18} independently are

- hydrogen, halogen, CN, $-CF_3$, $-OCF_3$, $-SCF_3$, -S(O) C_{1-6}-alkyl-, -C(O) C_{1-6}-alkyl-, C_{1-6}-alkyl, C_{1-6}-alkoxy, phenyl, cyclopentyl, cyclohexyl or phenoxy,

- or two of the groups R^{16} to R^{18} when placed in adjacent positions together may form a bridge $-O-(CF_2)_2-O-$, $-CF_2-O-CF_2-O-$ or $-O-CH_2-O-$.

In an embodiment the invention provides compounds, wherein E is



wherein R^{28}, R^{29}, R^{30}, R^{31} and R^{32} are independently selected from

- hydrogen,
- halogen, $-OCF_3$, $-OCHF_2$, $-SCF_3$, or $-CF_3$,
- C_{1-6}-alkyl, which may optionally be substituted with one or more substituents selected from fluoro, -CN, $-CF_3$, $-OCF_3$, $-OR^{35}$ and $-NR^{35}R^{36}$,
- cyclohexyl or cyclohex-1-enyl, which may optionally be substituted with one or more substituents selected from fluoro, -CN, $-CF_3$, $-OCF_3$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,
- phenyl which may optionally be substituted with one or more substitutents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,
- phenoxy or benzyloxy, of which the phenyl moieties may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,
- thiadiazolyl,

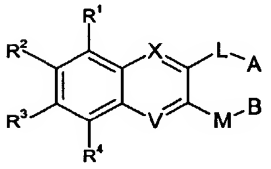
R^{35} and R^{36} independently are hydrogen or C_{1-6}-alkyl.

In an embodiment the invention provides compounds, wherein Y is –C=O-, $–CH_2$-.

In an embodiment the invention provides compounds, wherein Z is $–CH_2$-, -(C=O)-(NH), -(C=O)-O - or -(C=O)-CH_2-.

In an embodiment the invention provides a compound which is 3-{4-[(4-Cyclohexylbenzyl)-(4-trifluoromethoxybenzyl)amino]benzoylamino}propionic acid.

In an embodiment the invention provides a glucagon antagonist represented by the general formula (I):



(I)

wherein

R^1, R^2, R^3 and R^4 independently are hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^5$, lower alkyl, $-SR^5$, $-S(O)_2NR^5R^6$, $-S(O)NR^5R^6$, $-S(O)_2R^5$, $-S(O)R^5$, $-C(O)NR^5R^6$, $-CH_2OR^5$, $-CH_2NR^5R^6$, $-NR^5R^6$, $-C(O)R^5$ or $-C(O)OR^5$,

wherein R^5 and R^6 independently are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl, or R^5 and R^6 together with the nitrogen atom to which they are bound form a 3 to 8 membered heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur and optionally containing one or more double bonds,

in which the cycloalkyl, cycloalkenyl, heterocyclyl, aryl and heteroaryl rings may optionally be substituted with one or more substituents independently selected from halogen, lower alkyl, lower alkanoyl, -OH, $-CH_2OH$, $-NO_2$, -CN, -C(O)OH, -O-lower alkyl,

$-C(O)OCH_3$, $-C(O)NH_2$, $-OCH_2C(O)NH_2$, $-NH_2$, $-N(CH_3)_2$, $-CH_2N(CH_3)_2$, $-SO_2NH_2$, $-OCHF_2$, $-CF_3$ and $-OCF_3$,

one of X and V is =N-, and the other is =CD- or =N-,

wherein D is hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^7$, $-NR^7R^8$, lower alkyl, aryl, $-C(O)NR^7R^8$, $-CH_2OR^7$, $-CH_2NR^7R^8$ or $-C(O)OR^7$,

wherein R^7 and R^8 independently are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl, or R^7 and R^8 together with the nitrogen atom to which they are bound form a 3 to 8 membered heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur and optionally containing one or more double bonds,

in which the cycloalkyl, cycloalkenyl, heterocyclyl, aryl and heteroaryl rings may optionally be substituted with one or more substituents independently selected from halogen, lower alkyl, lower alkanoyl, -OH, $-CH_2OH$, $-NO_2$, -CN, -C(O)OH, -O-lower alkyl, $-C(O)OCH_3$, $-C(O)NH_2$, $-OCH_2C(O)NH_2$, $-NH_2$, $-N(CH_3)_2$, $-CH_2N(CH_3)_2$, $-SO_2NH_2$, $-OCHF_2$, $-CF_3$ and $-OCF_3$,

L and M independently are a valence bond, $-(CH_2)_mS(CH_2)_n-$, $-(CH_2)_mO(CH_2)_n-$, $-(CH_2)_mS(O)(CH_2)_n-$, $-(CH_2)_mS(O)_2(CH_2)_n-$, $-(CH_2)_mCH=CH(CH_2)_n-$, $-(CH_2)_mC\equiv C(CH_2)_n-$, $-(CH_2)_mCHR^9(CH_2)_n-$, $-(CH_2)_mNR^9(CH_2)_n-$, $-(CH_2)_mC(O)NR^9(CH_2)_n-$, $-(CH_2)_mC(O)O(CH_2)_n-$, $-S(CH_2)_mC(O)O(CH_2)_n-$, $-S(O)_2(CH_2)_mC(O)O(CH_2)_n-$, $-S(O)_2(CH_2)_mC(O)(CH_2)_n-$, $-S(O)_2NR^9(CH_2)_mC(O)O(CH_2)_n-$, $-S(CH_2)_mC(O)NR^9(CH_2)_n-$, $-(CH_2)_mOC(O)(CH_2)_n-$, $-(CH_2)_mC(O)(CH_2)_n-$, $-(CH_2)_mC(NOR^9)(CH_2)_n-$, $-(CH_2)_mNR^9S(O)_2(CH_2)_n-$, $-(CH_2)_mS(O)_2NR^9(CH_2)_n-$, $-(CH_2)_mCHOR^9(CH_2)_n-$, $-(CH_2)_mP(O)(OR^9)O(CH_2)_n-$, $-S(O)_2(CH_2)_mCONR^9(CH_2)_n-$, $-S(O)_2(CH_2)_mOC(O)NR^9(CH_2)_nC(O)O(CH_2)_r-$, $-NR^9O(CH_2)_n-$, $-NR^9NR^{9a}C(O)NR^{9b}(CH_2)_n-$, $-NR^9(CH_2)_mNR^{9a}C(O)(CH_2)_n-$ or $-NR^9(CR^{9c}R^{9d})_n-$,

wherein R^9, R^{9a} and R^{9b} independently are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-

lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl,

in which the cycloalkyl, cycloalkenyl, heterocyclyl, aryl and heteroaryl rings may optionally be substituted with one or more substituents independently selected from halogen, lower alkyl, lower alkanoyl, -OH, $-CH_2OH$, $-NO_2$, -CN, -C(O)OH, -O-lower alkyl, $-C(O)OCH_3$, $-C(O)NH_2$, $-OCH_2C(O)NH_2$, $-NH_2$, $-N(CH_3)_2$, $-CH_2N(CH_3)_2$, $-SO_2NH_2$, $-OCHF_2$, $-CF_3$ and $-OCF_3$,

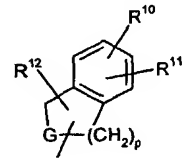
R^{9c} and R^{9d} independently are hydrogen or lower alkyl,

m, n and r independently are 0, 1, 2, 3 or 4,

A and B independently are hydrogen, halogen, $-CF_3$, $-CF_2CF_3$, -CN, $-NO_2$, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, hydroxy,

in which the cycloalkyl ring may optionally be substituted with one or more substituents independently selected from halogen, lower alkyl, lower alkanoyl, -OH, $-CH_2OH$, $-NO_2$, -CN, -C(O)OH, -O-lower alkyl, $-C(O)OCH_3$, $-C(O)NH_2$, $-OCH_2C(O)NH_2$, $-NH_2$, $-N(CH_3)_2$, $-CH_2N(CH_3)_2$, $-SO_2NH_2$, $-OCHF_2$, $-CF_3$ and $-OCF_3$,

or A and B independently are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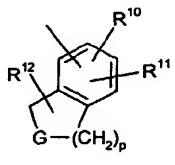
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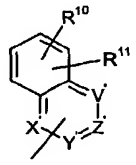
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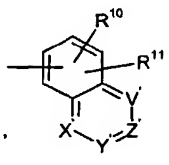
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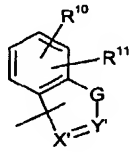
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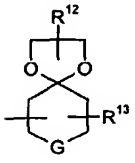
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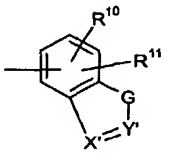
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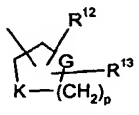
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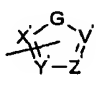
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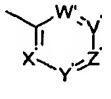
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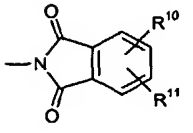
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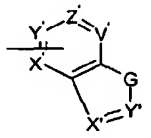
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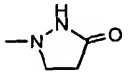
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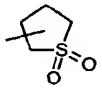


wherein

p is 1, 2 or 3,

X' is -N= or -CR^{14}=,

Y' is -N= or -CR^{15}=,

Z' is -N= or -CR^{16}=,

V' is -N= or -CR^{17}=,

W' is -N= or -CR^{18}=,

G is -$CR^{18a}R^{18b}$-, -N^+O^--, -NR^{19}-, -O- or -S-,

K is -$CR^{18c}R^{18d}$-, -NR^{20}, -O- or -S-,

R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{18a}, R^{18b}, R^{18c} and R^{18d} independently are hydrogen, halogen, -CN, -CF_3, -OCF_3, -OCH_2CF_3, -OCF_2CHF_2, -NO_2, -OR^{21}, -$NR^{21}R^{22}$, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl, -SCF_3, -SR^{21}, -CHF_2, -$OCHF_2$, -$OS(O)_2CF_3$, -$OS(O)_2R^{21}$, -$NR^{21}S(O)_2R^{22}$, -$S(O)_2NR^{21}R^{22}$, -$S(O)NR^{21}R^{22}$, -$S(O)_2R^{21}$, -$S(O)R^{21}$, -$CH_2C(O)NR^{21}R^{22}$, -$OCH_2C(O)NR^{21}R^{22}$, -CH_2OR^{21}, -$CH_2NR^{21}R^{22}$, -$OC(O)R^{21}$, -$S(O)_2NR^{21}(CH)_sC(O)OR^{22}$, -$C(O)NR^{21}(CH)_sC(O)OR^{22}$ or -$C(O)NR^{21}R^{22}$ where R^{12} and R^{13} furthermore independently may represent oxo, or two of the groups R^{10} to R^{18d} when defined in the same ring together may form a bridge -$O(CH_2)_qO$- or -$CH_2O(CH_2)_qO$-,

in which the cycloalkyl, cycloalkenyl, heterocyclyl, aryl and heteroaryl rings may optionally be substituted with one or more substituents independently selected from halogen, lower alkyl, lower alkanoyl, -OH, -CH_2OH, -NO_2, -CN, -C(O)OH, -O-lower alkyl,

$-C(O)OCH_3$, $-C(O)NH_2$, $-OCH_2C(O)NH_2$, $-NH_2$, $-N(CH_3)_2$, $-CH_2N(CH_3)_2$, $-SO_2NH_2$, $-OCHF_2$, $-CF_3$ and $-OCF_3$,

wherein R^{21} and R^{22} independently are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl, or R^{21} and R^{22} together with the nitrogen atom to which they are bound form a 3 to 8 membered heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur and optionally containing one or more double bonds,

in which the cycloalkyl, cycloalkenyl, heterocyclyl, aryl and heteroaryl rings may optionally be substituted with one or more substituents independently selected from halogen, lower alkyl, lower alkanoyl, -OH, $-CH_2OH$, $-NO_2$, -CN, -C(O)OH, -O-lower alkyl, $-C(O)OCH_3$, $-C(O)NH_2$, $-OCH_2C(O)NH_2$, $-NH_2$, $-N(CH_3)_2$, $-CH_2N(CH_3)_2$, $-SO_2NH_2$, $-OCHF_2$, $-CF_3$ and $-OCF_3$,

R^{19} and R^{20} independently are hydrogen, $-OR^{23}$, $-NR^{23}R^{24}$, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl, $-C(O)NR^{23}R^{24}$ or $-C(O)OR^{23}$,

in which the cycloalkyl, cycloalkenyl, heterocyclyl, aryl and heteroaryl rings may optionally be substituted with one or more substituents independently selected from halogen, lower alkyl, lower alkanoyl, -OH, $-CH_2OH$, $-NO_2$, -CN, -C(O)OH, -O-lower alkyl, $-C(O)OCH_3$, $-C(O)NH_2$, $-OCH_2C(O)NH_2$, $-NH_2$, $-N(CH_3)_2$, $-CH_2N(CH_3)_2$, $-SO_2NH_2$, $-OCHF_2$, $-CF_3$ and $-OCF_3$,

wherein R^{23} and R^{24} independently are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-

lower alkenyl or heteroaryl-lower alkynyl, or R^{23} and R^{24} together with the nitrogen atom to which they are bound form a 3 to 8 membered heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur and optionally containing one or more double bonds,

in which the cycloalkyl, cycloalkenyl, heterocyclyl, aryl and heteroaryl rings may optionally be substituted with one or more substituents independently selected from halogen, lower alkyl, lower alkanoyl, -OH, $-CH_2OH$, $-NO_2$, -CN, -C(O)OH, -O-lower alkyl, $-C(O)OCH_3$, $-C(O)NH_2$, $-OCH_2C(O)NH_2$, $-NH_2$, $-N(CH_3)_2$, $-CH_2N(CH_3)_2$, $-SO_2NH_2$, $-OCHF_2$, $-CF_3$ and $-OCF_3$,

q is 1, 2 or 3,

s is 0, 1, 2 or 3,

or

A and B may be connected and together form a C_{2-3}-alkylene radical,

with the provisos that

when L represents a group wherein n or r is 0, A is not halogen, -CN or $-NO_2$, and

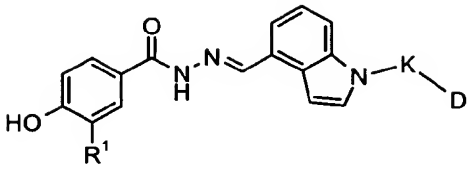
when M represents a group wherein n or r is 0, B is not halogen, -CN or $-NO_2$,

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these.

(S)-3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid or

(R)-3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

In an embodiment the invention provides glucagon antagonists represented by the general formula (I):



(I)

wherein

R^1 is chloro, fluoro, nitro or cyano;

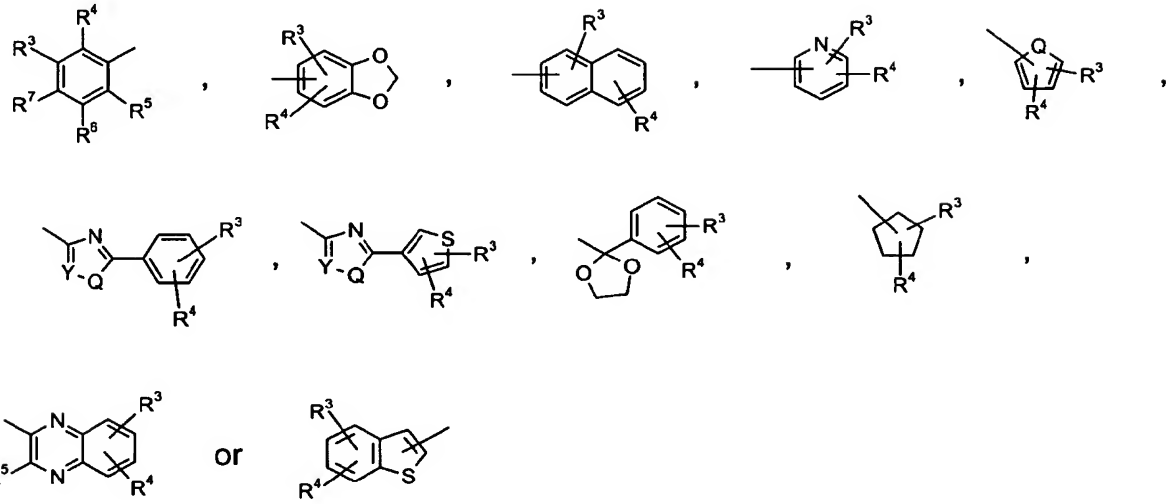
K is $-C(O)-(CH_2)_d-$, $-CH_2-CH_2-O-$ or $-CHR^2-$;

wherein

d is 0 or 1;

R^2 is hydrogen or C_{1-6}-alkyl ;

D is



wherein

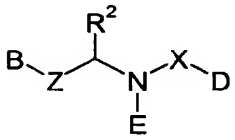
Q is -O- or -S-;

Y is -CH= or -N=;

R^3, R^4, R^5, R^6 and R^7 independently are hydrogen, C_{1-6}-alkyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, halogen, carboxamido, hydroxymethyl, phenyl, dimethylamino, C_{1-6}-alkoxy or nitro;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these.

In an embodiment, the invention provides a glucagon antagonist of the general formula (I):

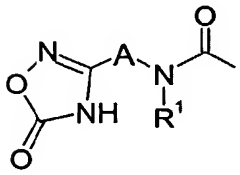


(I)

wherein

R^2 is hydrogen or C_{1-6}-alkyl,

B is



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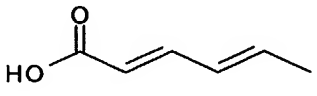

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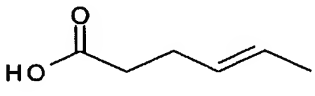
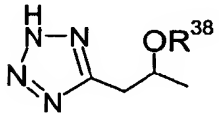


or



,

R^{38} is hydrogen, $-S(=O)_2-C_{1-6}$-alkyl or $-C(=O)-C_{1-6}$-alkyl,

A is a valence bond, $-(CR^3R^4)-$, or $-(CR^3R^4)(CR^5R^6)-$,

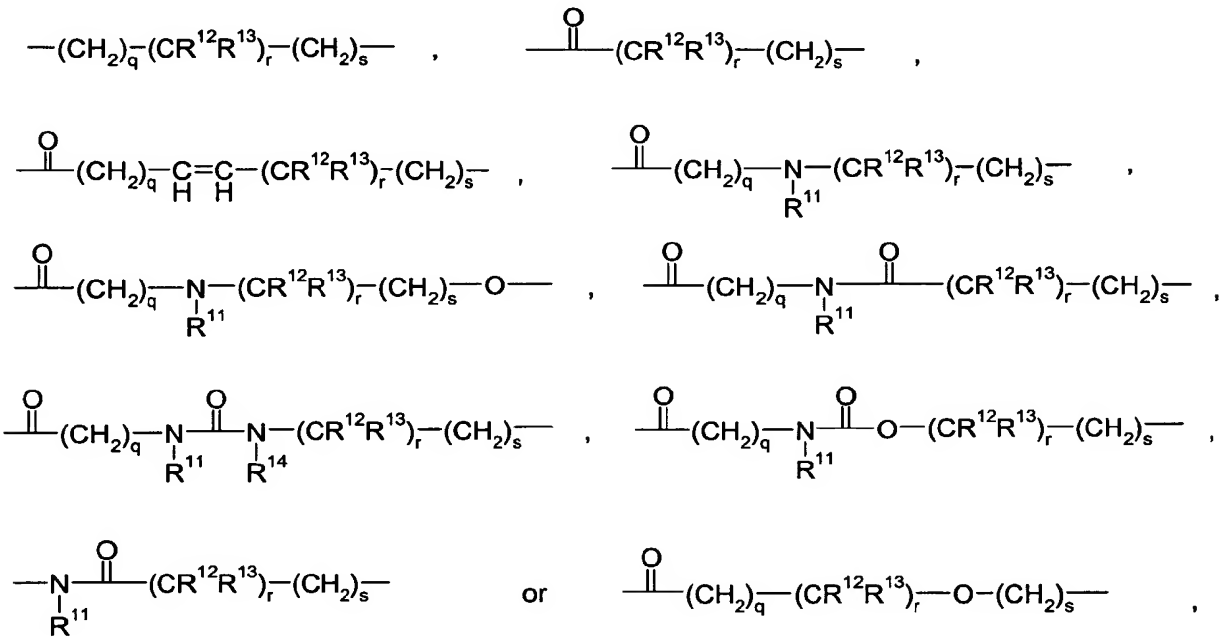
R^1, R^3, R^4, R^5 and R^6 independently are hydrogen or C_{1-6}-alkyl,

Z is arylene or a divalent radical derived from a 5 or 6 membered heteroaromatic ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur,

which may optionally be substituted with one or two groups R^7 and R^8 selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^9$, $-NR^9R^{10}$ and C_{1-6}-alkyl,

wherein R^9 and R^{10} independently are hydrogen or C_{1-6}-alkyl,

X is



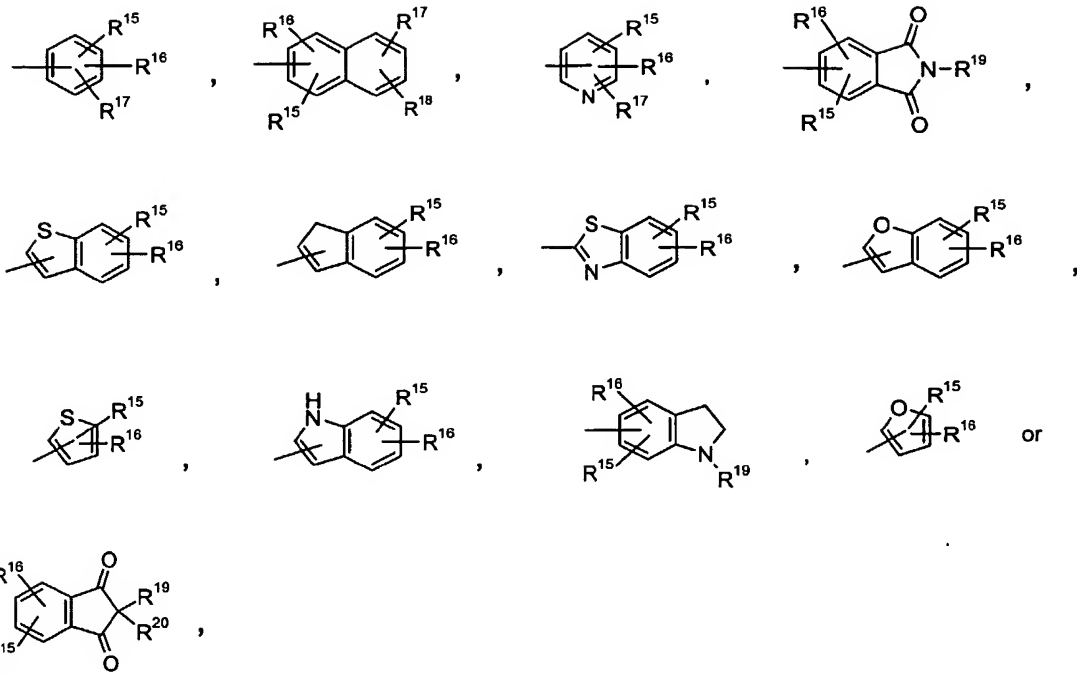
wherein

r is 0 or 1,

q and s independently are 0, 1, 2 or 3,

R^{11}, R^{12}, R^{13} and R^{14} independently are hydrogen or C_{1-6}-alkyl,

D is



wherein

R^{15}, R^{16}, R^{17} and R^{18} independently are

hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{21}$, $-NR^{21}R^{22}$, $-SR^{21}$, $-NR^{21}S(O)_2R^{22}$, $-S(O)_2NR^{21}R^{22}$, $-S(O)NR^{21}R^{22}$, $-S(O)R^{21}$, $-S(O)_2R^{21}$, $-C(O)NR^{21}R^{22}$, $-OC(O)NR^{21}R^{22}$, $-NR^{21}C(O)R^{22}$, $-CH_2C(O)NR^{21}R^{22}$, $-OCH_2C(O)NR^{21}R^{22}$, $-CH_2OR^{21}$, $-CH_2NR^{21}R^{22}$, $-OC(O)R^{21}$, $-C(O)R^{21}$ or $-C(O)OR^{21}$,

C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{21}$, $-NR^{21}R^{22}$ and C_{1-6}-alkyl,

C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkoxy, C_{3-8}-cycloalkyloxy, C_{3-8}-cycloalkyl-C_{1-6}-alkylthio, C_{3-8}-cycloalkylthio,

C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{21}$, $-NR^{21}R^{22}$ and C_{1-6}-alkyl,

wherein R^{21} and R^{22} independently are hydrogen, C_{1-6}-alkyl or aryl,

or R^{21} and R^{22} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{15} to R^{18} when placed in adjacent positions together may form a bridge $-(CR^{23}R^{24})_a-O-(CR^{25}R^{26})_c-O-$,

wherein

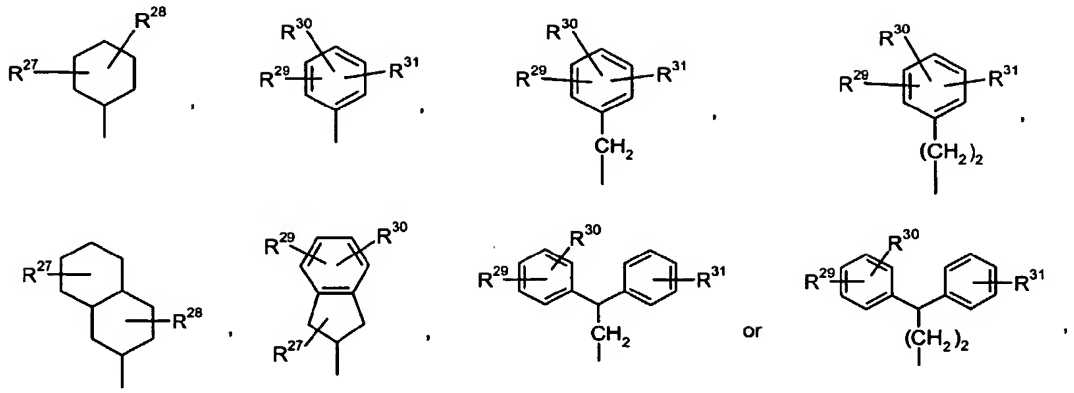
a is 0, 1 or 2,

c is 1 or 2,

R^{23}, R^{24}, R^{25} and R^{26} independently are hydrogen, C_{1-6}-alkyl or fluorine,

R^{19} and R^{20} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,

E is



wherein

R^{27} and R^{28} independently are

hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{32}$, $-NR^{32}R^{33}$, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl or aryl,

wherein the aryl group optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{32}$, $-NR^{32}R^{33}$ and C_{1-6}-alkyl,

wherein

R^{32} and R^{33} independently are hydrogen or C_{1-6}-alkyl, or

R^{32} and R^{33} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

R^{29}, R^{30} and R^{31} independently are

hydrogen, halogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{34}$, $-NR^{34}R^{35}$, $-SR^{34}$, $-S(O)R^{34}$, $-S(O)_2R^{34}$, $-C(O)NR^{34}R^{35}$, $-OC(O)NR^{34}R^{35}$, $-NR^{34}C(O)R^{35}$, $-OCH_2C(O)NR^{34}R^{35}$, $-C(O)R^{34}$ or $-C(O)OR^{34}$,

C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{34}$, $-NR^{34}R^{35}$ and C_{1-6}-alkyl,

C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{34}$, $-NR^{34}R^{35}$ and C_{1-6}-alkyl,

wherein R^{34} and R^{35} independently are hydrogen, C_{1-6}-alkyl or aryl,

or R^{34} and R^{35} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{29}, R^{30} and R^{31} when attached to the same ring carbon atom or different ring carbon atoms together may form a radical $-O-(CH_2)_t-CR^{36}R^{37}-(CH_2)_l-O-$, $-(CH_2)_t-CR^{36}R^{37}-(CH_2)_l-$ or $-S-(CH_2)_t-CR^{36}R^{37}-(CH_2)_l-S-$,

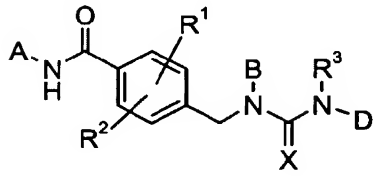
wherein

t and l independently are 0, 1, 2, 3, 4 or 5,

R^{36} and R^{37} independently are hydrogen or C_{1-6}-alkyl,

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these

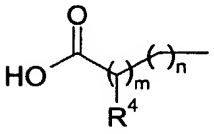
In an embodiment the invention provides glucagon antagonist of formula (I):



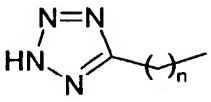
(I)

wherein

A is



or



,

m is 0 or 1,

n is 0, 1, 2 or 3,

with the proviso that m and n must not be 0 at the same time,

R^4 is hydrogen, fluoro or $-(CH_2)_p-OR^5$,

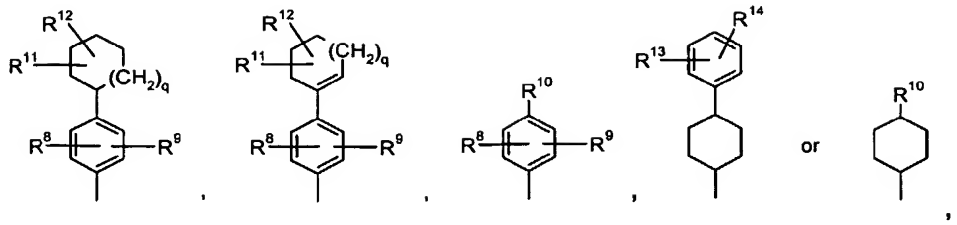
p is 0 or 1,

R^5 is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkanoyl, aryl or aryl-C_{1-6}-alkyl,

R^1 and R^2 independently are hydrogen, halogen, trifluoromethyl, trifluoromethoxy, cyano, trifluoromethylthio, nitro, C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, trifluoromethylsulfonyl or $-NR^6R^7$,

R^6 and R^7 independently are hydrogen or C_{1-6}-alkyl,

B is



R^8, R^9, R^{13} and R^{14} independently are hydrogen, halogen, trifluoromethyl, C_{1-6}-alkyl or C_{1-6}-alkoxy,

R^{10} is hydrogen, halogen, trifluoromethyl, trifluoromethoxy, cyano, trifluoromethylthio, nitro, C_{1-6}-alkyl, methylthio or C_{3-8}-cycloalkyl,

R^{11} and R^{12} independently are hydrogen or C_{1-6}-alkyl,

q is 0, 1, 2 or 3;

R^3 is hydrogen or C_{1-8}-alkyl,

X is =N-CN, =N-CH_2R^{15}, =CH-NO_2 or =CHR^{15},

R^{15} is

- hydrogen, cyano or trifluoromethyl,

- C_{1-6}-alkyl, which may optionally be substituted with

fluoro, trifluoromethyl, trifluoromethoxy, cyano, trifluoromethylthio, C_{1-6}-alkoxy, hydroxy, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, trifluoromethylsulfonyl or -$NR^{16}R^{17}$,

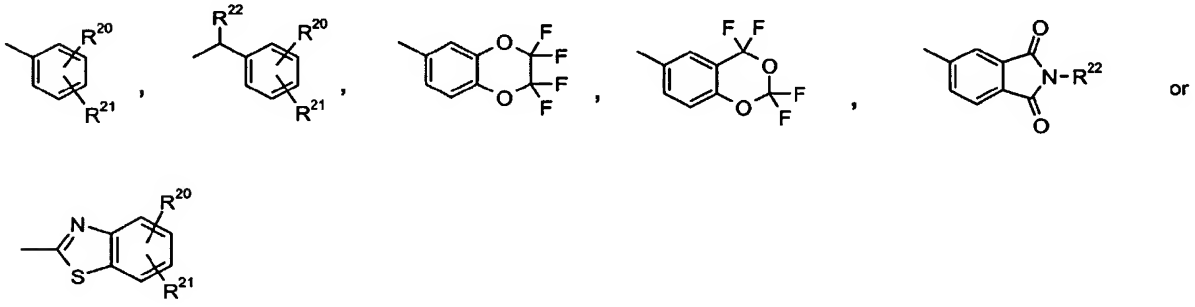
R^{16} and R^{17} independenly are hydrogen or C_{1-6}-alkyl,

• aryl or heteroaryl, which may optionally be substituted with

halogen, trifluoromethyl, trifluoromethoxy, cyano, trifluoromethylthio, nitro, C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, trifluoromethylsulfonyl or $-NR^{18}R^{19}$,

R^{18} and R^{19} independenly are hydrogen or C_{1-6}-alkyl,

D is



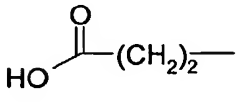
R^{20} and R^{21} independently are hydrogen, halogen, trifluoromethyl, trifluoromethoxy, cyano, trifluoromethylthio, nitro, C_{1-6}-alkyl, aryl, methylthio, methylsulfonyl, trifluoromethylsulfonyl, $-NR^{23}R^{24}$, C_{3-8}-cycloalkyl or $-S(O)_2-N(C_{1-6}\text{-alkyl})(aryl)$,

R^{23} and R^{24} independently are hydrogen or C_{1-6}-alkyl,

R^{22} is hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,

as well as any diastereomer or enantiomer or tautomeric form thereof including mixtures of these

In an embodiment the invention provides a compound, wherein A is



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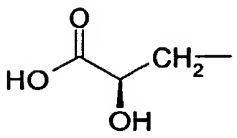
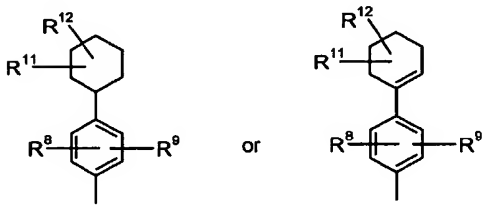
In an embodiment the invention provides a compound, wherein A is



In an embodiment the invention provides a compound, wherein R^1 and R^2 are both hydrogen.

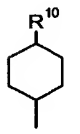
In an embodiment the invention provides a compound, wherein B is



wherein R^8, R^9, R^{11} and R^{12} are as defined above.

In an embodiment the invention provides a compound, wherein R^8 and R^9 are both hydrogen.

In an embodiment the invention provides a compound, wherein B is

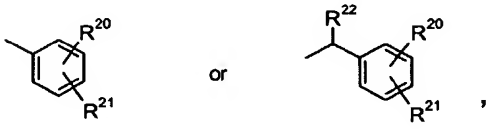


wherein R^{10} is as defined in above.

In an embodiment the invention provides a compound, wherein X is =N-CN, =CH-NO_2, =N-CH_2-CF_3 or =N-CH_2-CN.

In an embodiment the invention provides a compound, wherein R^3 is hydrogen.

In an embodiment the invention provides a compound, wherein D is



wherein R^{20}, R^{21} and R^{22} are as defined above.

In an embodiment the invention provides a compound, wherein R^{20} and R^{21} independently are hydrogen, halogen, trifluoromethyl or trifluoromethoxy, and R^{22} is C_{1-6}-alkyl.

In an embodiment the invention provides solvates of compounds as described above.

In an embodiment the invention provides 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}propionic acid in a solvate form.

In an embodiment the invention provides 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid in a solvate form.

In an embodiment the invention provides 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid as a solvate with one of the following solvents ethanol, 2-propanol, 2-methyl-1-propanol, n-butanol, 2-butanol, 3-methyl-1-butanol, diethyl ether, *tert*-butyl-methylether, tetrahydrofuran, anisol, acetone, 2-butanon, methylacetate, ethylacetate, n-propylacetate and toluene.

In an embodiment the invention provides *N*-[4-({4-(1-cyclohexen-1-yl)[(3,5-dichloroanilino)-carbonyl]anilino}methyl)benzoyl]-β-alanine as a solvate with acetone, butanol, ethanol or propanol.

In an embodiment the invention provides 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid as a solvate with 2-butanol, 3-methyl-1-butanol and 2-methyl-1-propanol.

In an embodiment the invention provides a process for the preparation a solvate of 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid comprising the steps of :

a) dissolving the parent compound as a free acid, an ester derivative or as a solvate of the parent compound, in same solvent as the solvate to be obtained or a different solvent or in a mixture of solvents

b) optionally heating the mixture

c) cooling the solution

d) isolating the precipitate

e) optionally drying the obtained solvate.

In an embodiment the invention provides the process of claim 4 wherein the temperature in the optional step b) is below 150 °C, optionally below 85°C.

In an embodiment the invention provides a pharmaceutical composition comprising, as an active ingredient a compound according to the invention as a solvate or as a salt as describedn above together with pharmaceutically acceptable carriers and/or diluents

In an embodiment the invention provides a pharmaceutical composition according to the above in a unit dosage form comprising from about 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg compound as described above.

In an embodiment the invention provides a pharmaceutical composition useful in the treatment and/or prevention of conditions mediated by glucagon receptors, the composition comprising a compound as a salt or as a solvate according to the above together with a pharmaceutically acceptable carrier or diluent.

A method for the treatment and/or prevention of conditions mediated by glucagon receptors which method comprises administering to a subject in need thereof an an effective amount of a compounds according to the above as a solvate or as a salt.

A method for the treatment and/or prevention of diabetes and/or obesity which method comprises administering to a subject in need thereof an effective amount of a compound according to the above.

The invention provides the use of a compound according to the above as a salt or as a solvate for the preparation of a medicament useful in the treatment and/or prevention of conditions mediated by glucagon receptors.

The invention provides the use of a compound according to the above for the preparation of a medicament useful in the treatment and/or prevention of diabetes and/or obesity.

Examples:

PXRD (Powder X-ray Diffraction)

The PXRD measurements were conducted on a Bruker D8 Advance powder diffractometer equipped with a multilayer mirror which selects the CuK_α radiation (λ = 1.5418 Å). The sample is mounted on a flat plate in reflection geometry in the center of a goniometer with a diameter of 435 mm. The diffracted beam from the sample is recorded stepwise with a scintillation detector. All samples were ground in an agate mortar before measurement.

Scan range in 2θ: 2°-30°

Step size: 0.03°

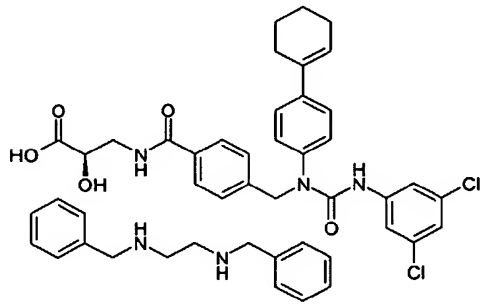
Time per step: 10 sec

Thermal Analysis

Differential Scanning Analysis (DSC) was conducted on a MDSC 2920, TA Instruments. Samples (approximately 3 – 6 mg) were heated in pinhole crimped aluminium pans from 25°C to 280°C at a rate of 10°C/min. The DSC measuring chamber was continuously purged with dry nitrogen during the runs and the instrument was routinely calibrated with indium and tin.

Thermo gravimetric Analysis (TGA) experiments were conducted on a TA Hi Res Thermo gravimetric Analyser, Model 2959. Samples (approximately 6-12 mg) were heated in an open platinum pan from 25°C to 250°C at a rate of 10°C/min. The TGA measuring chamber was continuously purged with dry nitrogen during the runs and the instrument was routinely calibrated with indium and aluminium.

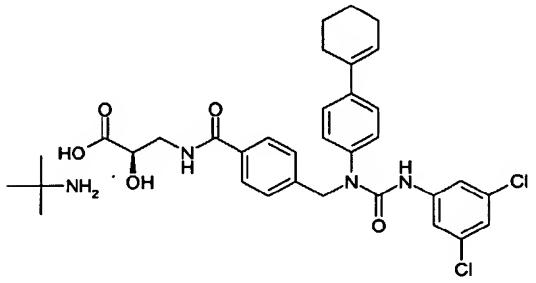
Example 1:[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]-benzoylamino}-2*R*-hydroxypropionic acid:*N,N'*-dibenzylethylenediamine (1:0.5)]



17.8g (0.03 mol) 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]-benzoylamino}-2*R*-hydroxypropionic acid, **1**, was dissolved in 350 ml ethyl acetate and 88 ml tetrahydrofurane under a nitrogen atmosphere. The solution was heated to 60°C. 3.68g

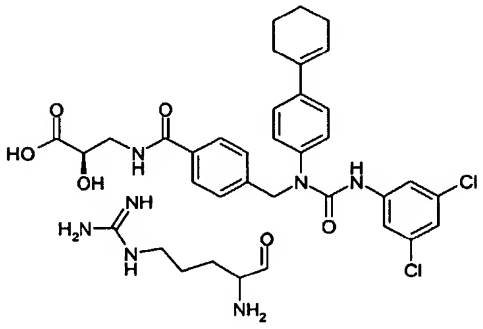
(0,015 mol) *N,N'*-dibenzyl-ethylenediamine was dissolved in 43 ml ethyl acetate, and added drop-wise to the hot solution over 20 minutes. When mixture became opaque, it was heated to 70°C and stirred at that temperature for 30 minutes. Then the mixture slowly cooled to room temperature, and the salt precipitated. The hemibenzathine salt was recovered and identified, after drying to constant weight.

Example 2: [3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]-benzoylamino}-2*R*-hydroxypropionic acid:*tert*-butyl amine (1:1)]



1.3.4 (0.582 g) was dissolved in acetone (8 ml) and *tert*-butylamine (105µl, 1.0 mmol in acetone) was added. More acetone was added (7 ml), and the solution was left to precipitate at room temperature. The suspension was cooled to 8°C over 2h, and the tert-butylamine salt of 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid was isolated. 0.51g was isolated after drying *in vacuo*.

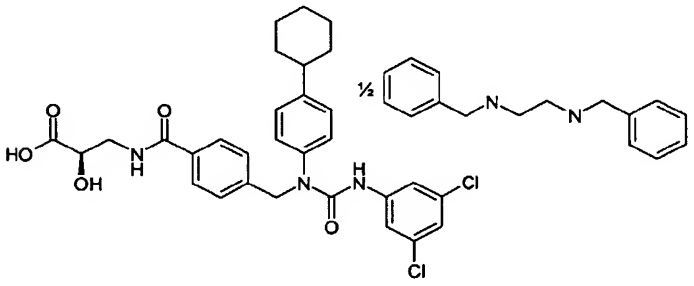
Example 3: [3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]-benzoylamino}-2*R*-hydroxypropionic acid:L-arginine (1:1)]



1 (29.15 mg, 0.050 mmole) was dissolved in methanol (1.0 mL) by heating. 520 µL (0.052 mmole) of a 0.100 M solution of L-arginine in MilliQ water was added. A fine, white precipitate was observed. The solution was stored at 4°C for 2 days, after which an apparently crystalline precipitate had formed. The mother liquor was filtered off and the precipitate was dried

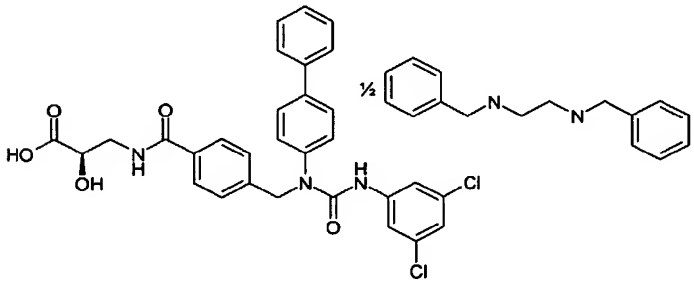
in a desiccator overnight. The precipitate had then become glass-like. This precipitate was analysed.

Example 4: (*2R*)-*N*-[4-({4-cyclohexyl[(3,5-dichloroanilino)carbonyl]anilino}methyl)-benzoyl]-2-hydroxy-*β*-alanine: *N,N'*-dibenzylethylenediamine (1:0.5)]



(2.4 g) was dissolved in isopropyl acetate (37 ml) and *N,N'*-dibenzyl-ethylenediamine (1.6 g, 6.5 mmol) in THF (18 ml) was added at elevated temperature. The solution was left to precipitate at room temperature. The suspension was cooled to 5°C, and the hemibenzathine salt of (*2R*)-*N*-[4-({4-cyclohexyl[(3,5-dichloroanilino)carbonyl]anilino}methyl)benzoyl]-2-hydroxy-*β*-alanine was isolated. 5.5 g was isolated after drying *in vacuo*.

Example 5: (*2R*)-*N*-[4-({[1,1'-biphenyl]-4-yl[(3,5-dichloroanilino)-carbonyl]amino}methyl)benzoyl]-2-hydroxy-*β*-alanine: *N,N'*-dibenzylethylenediamine (1:0.5)]



(*2R*)-*N*-[4-({[1,1'-biphenyl]-4-yl[(3,5-dichloroanilino)carbonyl]amino}methyl)benzoyl]-2-hydroxy-*β*-alanine (5.5 g) was dissolved in ethyl acetate (100 ml) and THF (28 ml) *N,N'*-dibenzyl-ethylenediamine (1.1 g, 4.7 mmol) in ethyl acetate (22 ml) was added at elevated temperature. The solvent was removed under reduced pressure. To the material hot methyl tert butyl ether was added, and the hemibenzathine salt of (*2R*)-*N*-[4-({[1,1'-biphenyl]-4-yl[(3,5-dichloroanilino)carbonyl]amino}methyl)benzoyl]-2-hydroxy-*β*-alanine precipitated. 5.7 g was isolated after drying *in vacuo*.

Example 6: 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]-benzoylamino}propionic acid : tert-butylamine:

582 mg 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]-benzoylamino}propionic acid was dissolved in 20-25 ml acetone. 0.105 ml *tert*-butylamine (1 eq.) was added slowly, and the reaction mixture was stirred at ambient temperature for 4 days. The suspension (Approx. 10-15 ml) was cooled 8°C over 2 hours and filtered. The crystals were washed with cold acetone and dried under vacuum. Yield: 78%

Example 7: 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]-benzoylamino}propionic acid :L-arginine:

566 mg. 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]-benzoylamino}propionic acid was dissolved in 15 ml 1-propanol at reflux. 174 Mg. *L*-arginine was dissolved in 1 ml H_2O by heating. The solution of *L*-arginine was slowly added to the solution of 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]-benzoylamino}propionic acid. Seeding crystals were added until crystallization was observed (At ca. 60°C), and the reaction mixture was cooled to ambient temperature over 1½ hour. The crystals were isolated by filtration, washed with 1-propanol and dried under vacuum. Yield: 73%.

Example 8: N3-(4-{[[4-(3,4-Dichlorophenyl)thiazol-2-yl]-(5,6,7,8-tetrahydronaphthalen-2-yl)amino]methyl}benzoylamino)propionic acid :tert-butylamine (erbumine) (1:1)

35.0 mg of 3-(4-{[[4-(3,4-Dichlorophenyl)thiazol-2-yl]-(5,6,7,8-tetrahydronaphthalen-2-yl)amino]methyl}benzoylamino)propionic acid
was dissolved in 2 mL ethylacetate with light heating. When dissolved, 620 µL of 0.097 M tert-butylamine in ethylacetate was added in three portions. The solution was allowed standing at room temperature a few days, during which an oily precipitate formed. This precipitate was dissolved in 1 mL THF (tetrahydrofurane) and again allowed standing at room temperature. After some days a crystalline precipitate formed.

Example 9: 3-(4-{[[4-(4-Chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)amino]methyl}benzoylamino)propionic acid: L-lysine (1:1)

33.7 mg of 3-(4-{[[4-(4-Chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)amino]methyl}-benzoylamino)propionic acid was dissolved in 1 mL of THF while shaking. 600 µL of 0.051 M

L-lysine in H_2O was added in three portions. The solution was allowed standing at room temperature a few days during which the solvent evaporated and an oily precipitate formed. This was dissolved in 1 mL of absolute ethanol, and after some days a white precipitate in the solution was formed. This slurry was dried on the sample holder and analysed.

Example 10: 3-(4-{[[4-(4-Chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)amino]-methyl}benzoylamino)propionic acid: L-histidine (1:1)

33.7 mg of 3-(4-{[[4-(4-Chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)amino]methyl}-benzoylamino)propionic acid was dissolved in 1 mL of THF while shaking. 600 µL of 0.050 M L-histidine in H_2O was added in three portions. The solution was allowed standing at room temperature a few days during which the solvent evaporated and an oily precipitate formed. This was dissolved in 1 mL of absolute ethanol, and after some days crystalline precipitate was formed on the side of the vial. The precipitate was analysed.

Example 11: 3-(4-{[[4-(4-Chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)-amino]methyl}benzoylamino)propionic acid :monoethanolamine (olamine) (1:1)

33.7 mg of 3-(4-{[[4-(4-Chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)amino]methyl}-benzoylamino)propionic acid was dissolved in 1 mL of ethylacetate while shaking. 575 µL of 0.104 M monoethanolamine in ethylacetate was added in three portions. The solution was allowed standing at room temperature. After one day a white, gel-like precipitate formed. This was suspended in 300 µL of ethylacetate. After some days a white precipitate was formed. The precipitate was analysed.

Example 12: 3-(4-{[[4-(4-Chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)-amino]methyl}benzoylamino)propionic acid: tert-butylamine (1:1)

33.6 mg of 3-(4-{[[4-(4-Chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)amino]methyl}-benzoylamino)propionic acid was dissolved in 1 mL of THF while shaking. 300 µL of 0.201 M tert-butylamine in ethanol was added in three portions. The solution was allowed standing at room temperature. After a few days a transparent, oily precipitate formed. This was dissolved in 1 mL of absolute ethanol. After some days a crystalline precipitate was formed. The precipitate was analysed.

Example 13: 3-(4-{[[4-(4-Chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)-amino]methyl}benzoylamino)propionic acid: ethylenediamine (2:1)

33.7 mg of 3-(4-{[[4-(4-Chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)amino]methyl}-benzoylamino)propionic acid was dissolved in 1 mL of ethylacetate while shaking. 510 µL of 0.118 M ethylenediamine in ethylacetate was added in three portions, during which a precipitate formed. The solution was allowed standing at room temperature. After a few days a white voluminous precipitate formed. This was suspended in 300 µL of ethylacetate. After some days a white, solid precipitate was formed. The precipitate was analysed.

Example 14: 3-(4-{[[4-(4-Chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)-amino]methyl}benzoylamino)propionic acid, dibenzylethylenediamine (benzathine) (2:1)

33.6 mg of 3-(4-{[[4-(4-Chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)amino]methyl}-benzoylamino)propionic acid was dissolved in 1 mL of THF while shaking. 290 µL of 0.104 M benzathine in ethanol was added in three portions. The solution was allowed standing at room temperature a few days during which the solvent evaporated and a solid, white precipitate formed. This was suspended in 1 mL of absolute ethanol, and after some days crystalline precipitate was formed. The precipitate was analysed.

General procedure for the preparation of solvates of the invention:

The parent compound as a free acid, an ester derivative or optionally as a solvate, was dissolved in a suitable solvent. The solvent may the same solvent as the solvate to be obtained or it may be a different solvent. Optionally the temperature was elevated to dissolve the compound. Also the pH may be adjusted for ensuring the compound was dissolved. Afterwards the solvent to form solvates with the compound as above was added in surplus amount and the formed solvate was isolated and dried, optionally *in vacuo*, at elevated temperature.

DSC method

The following instrumentation was used:

- Mettler Toledo DSC module 822
- Power Point Labplant RP 60 intra cooler
- Mettler Tolede DSC software STAR

A linear heating program from 25°C to 300°C with a heating rate of 10°C/min was used. The DSC experiments were performed in open lid 40 µl aluminum crucibles.

PXRD (Powder X-ray Diffraction)

The PXRD measurements were conducted on a Bruker D8 Advance powder diffractometer equipped with a multilayer mirror which selects the CuK_α radiation (λ = 1.5418 Å). The sample is mounted on a flat plate in reflection geometry in the center of a goniometer with a diameter of 435 mm. The diffracted beam from the sample is recorded stepwise with a scintillation detector. All samples were ground in an agate mortar before measurement.

Scan range in 2θ: 2°-30°

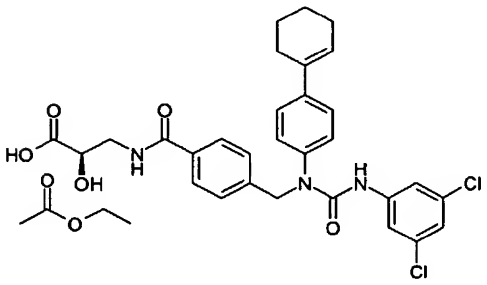
Step size: 0.03°

Time per step: 10 sec

Examples

Example 1

[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid:ethyl acetate]

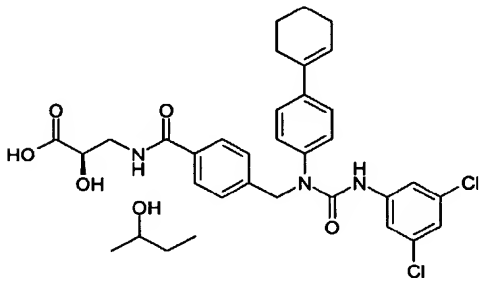


To a solution of methyl 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)-ureidomethyl]benzoylamino}-2*R*-hydroxypropionate (112 g) dissolved in THF (2800 ml) was added an aqueous solution of lithium hydroxide mono hydrate (10.2 g in 100 ml water). The mixture was stirred for 1 hour at room temperature. Phosphoric acid (3 M) was added to pH 2.4. Ethyl acetate (400 ml) was added to the solution and the two phases were separated. The organic phase was washed with water (200 ml), and the organic solvent was removed under reduced pressure. The evaporation residue was added ethyl acetate (500 ml) and further stripping of water conducted by removal of the solvent under reduced pressure. The crude material was dissolved in ethyl acetate (500 ml) and heated to 40 °C for 1 hour. The

solution was cooled to room temperature. After stirring over night a precipitate was formed and the slurry was cooled to 0°C prior to filtration. The filter cake was washed with cooled (2 °C) ethyl acetate (100 ml) and dried *in vacuo* at 40 °C for 2 hours followed by drying at room temperature in the air. The title compound (92.8 g) was isolated in 91% yield.

Example 2

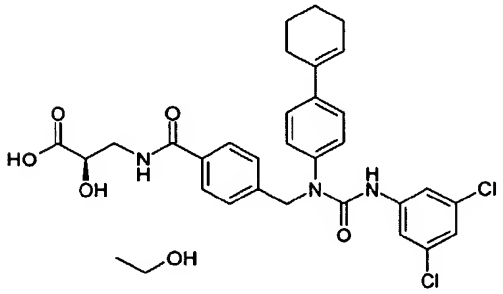
[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid:2-butanol]



1 (11.7 g) was dissolved in 2-butanol (75 ml) by heating. The 2-butanol solvate of 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid precipitated by stirring the mixture at room temperature. 7.6 g was isolated after drying the material *in vacuo* at 40 °C.

Example 3

[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid:ethanol]

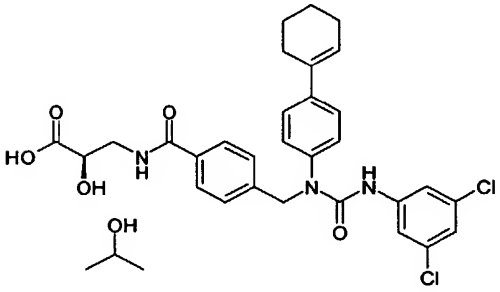


2 (5.0 g) was dissolved in ethanol (14 ml) by heating. Up on cooling to room temperature the ethanol solvate of 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid precipitated. The sus-

pension was filtered and washed with cold ethanol. After drying over night at room temperature 2.6g (52%) was isolated after drying the material at room temperature over night.

Example 4

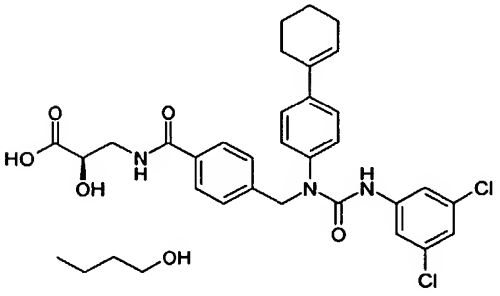
[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid:2-propanol]



2 (5.0 g) was dissolved in 2-propanol (12 ml) by heating. The 2-propanol solvate of 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid precipitated by stirring the mixture at room temperature. 1.0 g was isolated after drying the material at room temperature over night.

Example 5

[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid:1-butanol]

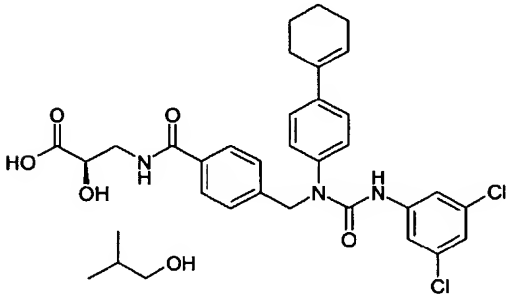


1 (5.0 g) was dissolved in 1-butanol (5 ml) by heating to 40 °C. n-Heptane (2.2 ml) was added and the 1-butanol solvate of 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid precipitated by cooling

to 20 – 25 °C. The suspension was filtered and washed with n-heptane (2 x 10 ml) followed by drying *in vacuo* at 40 °C for 5 days.

Example 6

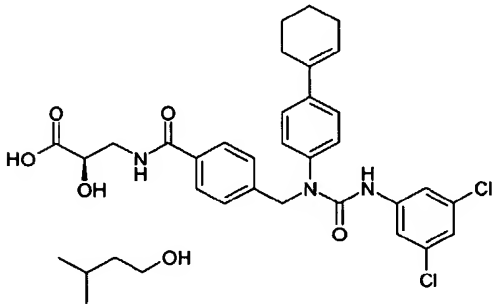
[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid:2-methyl-1-propanol]



1 (25.0 g) was dissolved in 2-methyl-1-propanol (50 ml) by heating to 40 °C. The 2-methyl-1-propanol solvate of 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]-benzoylamino}-2*R*-hydroxypropionic acid precipitated by cooling to 20 – 25 °C. The suspension was filtered and washed with 2-methyl-1-propanol (5 ml). Drying *in vacuo* at 40 °C for 2 days gave 21.4 g solvate.

Example 7

[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid:3-methyl-1-butanol]

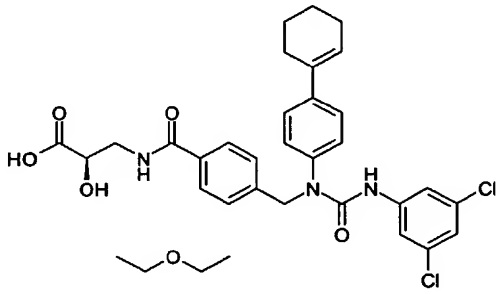


1 (5.0 g) was dissolved in 3-methyl-1-butanol (20 ml) by heating to 40 °C. The 3-methyl-1-butanol solvate of 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]-benzoylamino}-2*R*-hydroxypropionic acid precipitated by cooling to 20 – 25 °C. The suspen-

sion was filtered and washed with 3-methyl-1-butanol (10 ml) followed by drying *in vacuo* at 40 °C for 24 hours.

Example 8

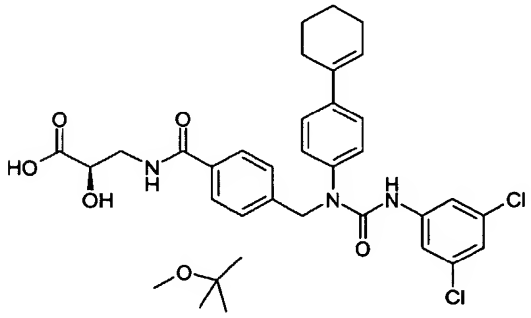
*[*3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid:diethyl ether]



1 (5.0 g) was partly dissolved in diethyl ether (15 ml) by heating. The diethyl ether solvate of 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid precipitated by cooling to 20 – 25 °C. After drying at room temperature for several days 4.3g was isolated.

Example 9

[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid:*tert*-butyl methyl ether]

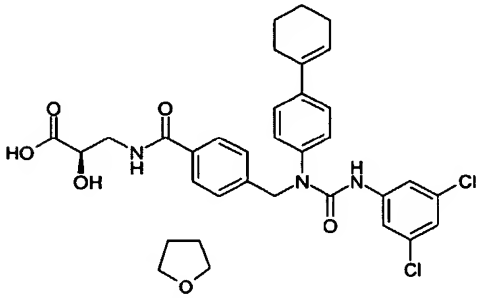


1 (5.0 g) was dissolved in *tert*-butyl methyl ether (7 ml) by heating to 40 °C. The *tert*-butyl methyl ether solvate of 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)-ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid precipitated by cooling to 20 – 25 °C.

The suspension was filtered and washed with n-heptane (2 x 10 ml) followed by drying *in vacuo* at 40 °C for 4 days.

Example 10

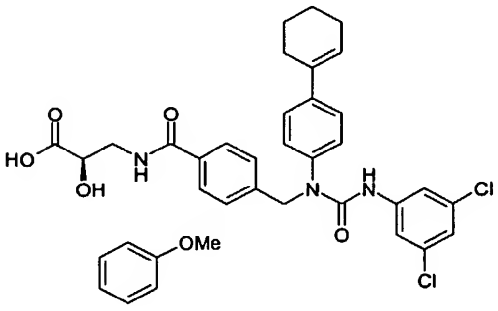
[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid:THF



1 (5.0 g) was dissolved in THF (5.0 ml) by heating to 35 °C. n-Heptane (8.0 ml) was added to the solution and the THF solvate of 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)-ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid precipitated by cooling to 20 – 25 °C. The suspension was filtered and the filter cake was dried at 20 – 25 °C for 6 days.

Example 11

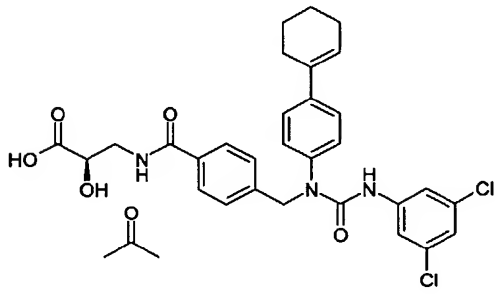
[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid:anisole]



1 (5.0 g) was dissolved in a mixture of THF (10 ml) and anisole (90 ml) by heating to 40 °C. The anisole solvate of 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)-ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid precipitated by cooling to 20 – 25 °C. The suspension was filtered and the product was washed with n-heptane (5 ml) followed by drying at 20 – 25 °C for 5 days.

Example 12

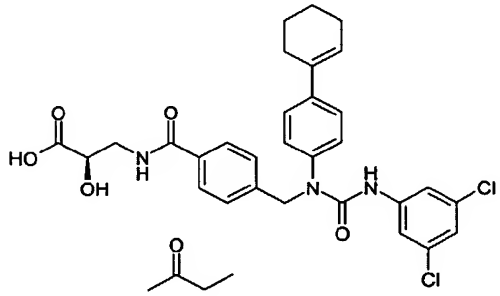
[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid:acetone]



1 (5.0 g) was dissolved in acetone (5.5 ml) by heating to 35 °C. n-Heptane (2.2 ml) was added to the solution and the acetone solvate of 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid precipitated by cooling to 20 – 25 °C. The suspension was filtered and the product was dried at 20 – 25 °C for 2 days.

Example 13

[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid: 2-butanone]

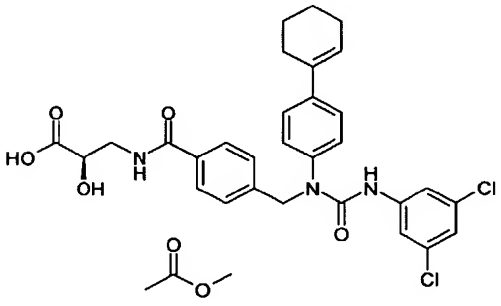


Methyl 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionate (9.0 g) dissolved in THF (80 ml) was hydrolysed with lithium hydroxide mono hydrate (0.75 g) dissolved in water (7.5 ml). The aqueous solution was added in 5 min, and the reaction mixture was stirred at room temperature for two hours. Hydrochloric acid (3

M) was added to pH 2.2 and ethyl acetate (50 ml) was added. The two phases were separated and the organic phase was washed with water (2 x 20 ml). The organic solvent was removed under reduced pressure. Water residues were removed by stripping with 2-butanone (2 x 50 ml). The crude material was dissolved in 2-butanone (90 ml) and heated to 50°C. The solution was added n-heptane (100 ml) and cooled to 5 °C. After stirring over night a precipitate was formed, and the title compound was isolated. The material was dried at 20 – 25 °C for 4 days.

Example 14

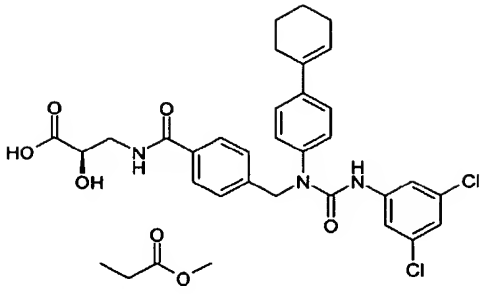
[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid: methyl acetate]



1 (5 g) was dissolved in methyl acetate (5 ml) at 40°C. At room temperature the methyl acetate solvate of 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]-benzoylamino}-2*R*-hydroxypropionic acid precipitated. The mixture was diluted with methyl acetate (5 ml) prior to filtration. The solvate was identified after drying at room temperature for 18 hours.

Example 15

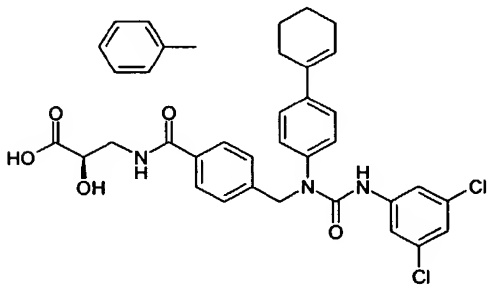
[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid:n-propyl acetate]



1 (5 g) was suspended in n-propyl acetate (15 ml). The material dissolved upon heating to 40°C to 45°C. The n-propyl acetate solvate of 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid precipitated by cooling to 0 - 5°C and was identified after drying at room temperature for 18 hours.

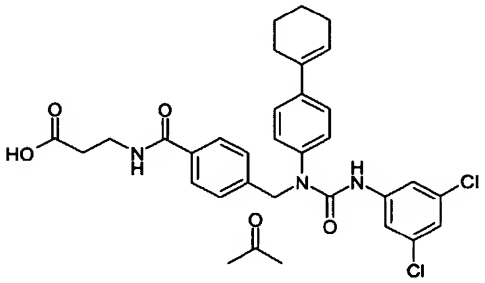
Example 16

[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid:toluene]



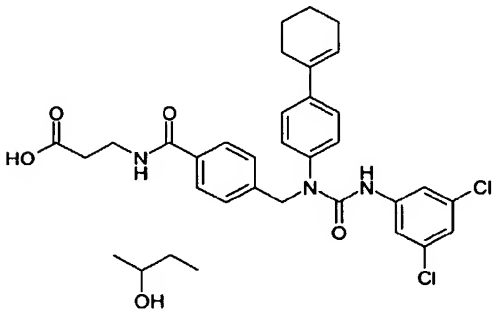
To a solution of methyl 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)-ureidomethyl]benzoylamino}-2*R*-hydroxypropionate (72 g) dissolved in ethanol (580 ml) and toluene (56 ml) was added an aqueous solution of lithium hydroxide mono hydrate (10.2 g in 100 ml water). The mixture was stirred for 1 hour at room temperature. Phosphoric acid (3 M) was added to adjust pH to 2.4. The mixture was heated to 40 °C for ½ hour. The solution was cooled to room temperature during 2 hours and kept at this temperature for 2 hours. Stirring over night at 10 °C resulted in formation of a white precipitate. The slurry was filtered and the filter cake was washed with cooled (10 °C) ethanol/water 1/1 (v/v) (2 x 70 ml) and dried *in vacuo* at 40 °C for 22 hours. The title compound (72.5 g) was isolated in 88% yield.

Example 17: *N*-[4-({4-(1-cyclohexen-1-yl)[(3,5-dichloroanilino)carbonyl]anilino}methyl)-benzoyl]-*β*-alanine:acetone



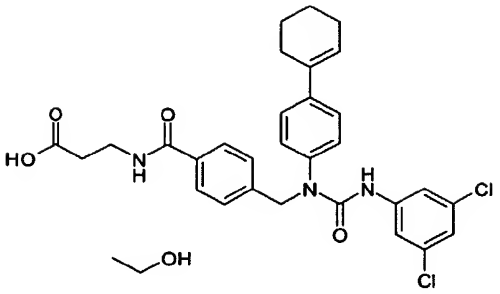
N-[4-({4-(1-cyclohexen-1-yl)[(3,5-dichloroanilino)carbonyl]anilino}methyl)benzoyl]-*β*-alanine (1.0 g) was dissolved in acetone (44 ml) by heating. The acetone solvate of *N*-[4-({4-(1-cyclohexen-1-yl)[(3,5-dichloroanilino)carbonyl]anilino}methyl)benzoyl]-*β*-alanine precipitated by stirring the mixture at room temperature. 0.62 g was isolated after drying the material.

Example 18:*N*-[4-({4-(1-cyclohexen-1-yl)[(3,5-dichloroanilino)carbonyl]anilino}-methyl)benzoyl]-*β*-alanine:2-butanol]



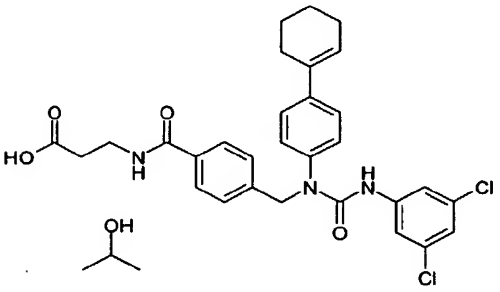
N-[4-({4-(1-cyclohexen-1-yl)[(3,5-dichloroanilino)carbonyl]anilino}methyl)benzoyl]-*β*-alanine (1.0 g) was dissolved in 2-butanol (44 ml) by heating. Up on cooling to room temperature the 2-butanol solvate of *N*-[4-({4-(1-cyclohexen-1-yl)[(3,5-dichloroanilino)carbonyl]anilino}-methyl)benzoyl]-*β*-alanine precipitated. The material was collected by filtration. After drying at room temperature 0.98 g was isolated.

Example 19: *N*-[4-({4-(1-cyclohexen-1-yl)[(3,5-dichloroanilino)carbonyl]anilino}methyl)-benzoyl]-*β*-alanine:ethanol]



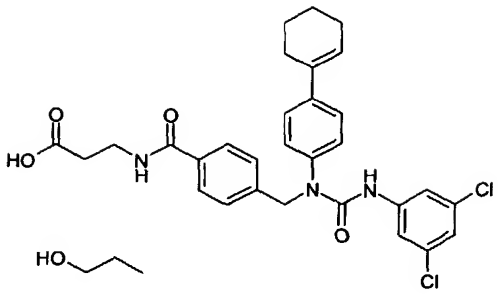
N-[4-({4-(1-cyclohexen-1-yl)[(3,5-dichloroanilino)carbonyl]anilino}methyl)benzoyl]-β-alanine (1.0 g) was dissolved in ethanol (36 ml) by heating. Up on cooling to room temperature the ethanol solvate of *N*-[4-({4-(1-cyclohexen-1-yl)[(3,5-dichloroanilino)carbonyl]anilino}-methyl)benzoyl]-β-alanine precipitated. The suspension was filtered and washed with cold ethanol. After drying for 2 days at room temperature 0.68g was isolated.

Example 20: *N*-[4-({4-(1-cyclohexen-1-yl)[(3,5-dichloroanilino)carbonyl]anilino}methyl)-benzoyl]-β-alanine:2-propanol]



N-[4-({4-(1-cyclohexen-1-yl)[(3,5-dichloroanilino)carbonyl]anilino}methyl)benzoyl]-β-alanine (1.0 g) was dissolved in 2-propanol (56 ml) by heating. The 2-propanol solvate of *N*-[4-({4-(1-cyclohexen-1-yl)[(3,5-dichloroanilino)carbonyl]anilino}methyl)benzoyl]-β-alanine precipitated by stirring the mixture at room temperature. 0.58 g was isolated after drying the material at room temperature over 3 days.

Example 21: *N*-[4-({4-(1-cyclohexen-1-yl)[(3,5-dichloroanilino)carbonyl]anilino}-methyl)benzoyl]-β-alanine:1-propanol]



N-[4-({4-(1-cyclohexen-1-yl)[(3,5-dichloroanilino)carbonyl]anilino}methyl)benzoyl]-*β*-alanine (1.0 g) was dissolved in 1-propanol (44 ml) by heating. The 2-propanol solvate of *N*-[4-({4-(1-cyclohexen-1-yl)[(3,5-dichloroanilino)carbonyl]anilino}methyl)benzoyl]-*β*-alanine precipitated by stirring the mixture at room temperature. 0.63 g was isolated after drying the material at room temperature over 3 days.

Measurement of stability:

The stability has been observed at accelerated as well as at long term storage conditions for a time period of 33 weeks. From the apparent degradation rates observed at the different storage conditions a retest time was estimated in the cases where a significant degradation was observed.

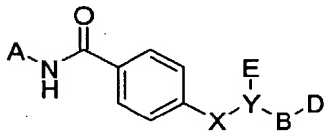
The experiment are measured at different temperatures and humidities for example: 25°C/60 % RH, 40°C/75% RH, 60°C/ambient humidity, or with light exposure in either open containers or bulk container.

CLAIMS

1. A composition comprising a salt of a glucagon antagonist and a pharmaceutically acceptable base.

2. The composition of claim 1, wherein the pharmaceutically acceptable basic counter ion is derived from ammonium or imidazole or the metal ions of lithium, sodium, potassium, magnesium, calcium, zinc, or the basic amino acids L-arginine, L-lysine, L-histidine, and L-ornithine; or alkylated ammonium derivatives such as di-ethylamine, tert-butylamine (erbumine), 1,2-ethylenediamine, N-(phenylmethyl)-benzeneethaneamine (benethamine) or N,N'-dibenzylethylenediamine (benzathine); or hydroxyalkylated ammonium derivatives trishydroxymethylaminomethane (tris, tromethamine), N-methyl-D-glucamine (meglumine), choline, monoethanolamine (2-aminoethanol, olamine), di-ethanolamine (2,2'-iminobis(ethanol)), tri-ethanolamine (2,2',2''-nitrilotris(ethanol), trolamine), 2-diethylaminoethanol.

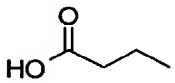
3. A composition according to claims 1 - 2, wherein the compound is represented by the general formula (I) below:



(I)

wherein

A is



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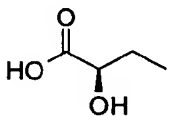
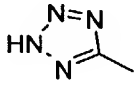


or



,

X is a valence bond, $-CR^1R^2-$ or $-NR^1-$,

Y is $>CR^3-$ or >N-,

R^1, R^2 and R^3 independently are hydrogen or C_{1-6}-alkyl, or R^1 and R^3 on adjacent atoms may be combined to form a double bond,

E is

- C_{1-10}-alkyl or C_{2-10}-alkenyl,

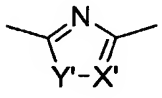
- C_{3-10}-cycloalkyl, C_{3-10}-cycloalkenyl, C_{7-10}-bicycloalkyl, C_{3-10}-cycloalkyl-C_{1-6}-alkyl, C_{3-10}-cycloalkenyl-C_{1-6}-alkyl or C_{7-10}-bicycloalkyl-C_{1-6}-alkyl,

wherein the rings may optionally be substituted with one or more substituents selected from halogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{1-6}-alkoxy, C_{1-6}-thioalkyl, $-CF_3$, $-OCF_3$, $-SCF_3$, $-OCHF_2$ and $-SCHF_2$,

- aryl, aryloxy, arylthio, heteroaryl, aryl-C_{1-6}-alkyl, aryloxy-C_{1-6}-alkyl, arylthio-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, diaryl-C_{1-6}-alkyl or (C_{1-6}-alkyl)(aryl)-C_{1-7}-alkyl,

wherein the non-aromatic and aromatic rings may optionally be substituted with one or more substituents selected from halogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{1-6}-alkoxy, C_{1-6}-thioalkyl, $-CF_3$, $-OCF_3$, $-SCF_3$, $-OCHF_2$, $-SCHF_2$, C_{3-10}-cycloalkyl and C_{3-10}-cycloalkenyl, or with two substituents on adjacent positions which are combined to form a bridge C_{1-6}-alkylene, C_{2-6}-alkenylene or $-O-C_{1-6}$-alkylene-O-,

B is



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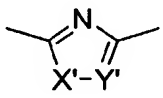

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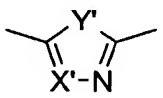

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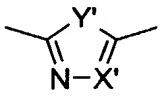

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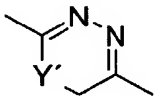


,

X' is -N= or $-CR^8$=,

Y' is -S-, -O- or $-NR^9$-,

R^8 is hydrogen, C_{1-6}-alkyl or aryl, wherein aryl is optionally substituted with one or two substituents selected from halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-thioalkyl, $-CF_3$, $-OCF_3$, $-SCF_3$, $-OCHF_2$, $-SCHF_2$, $-SO_2CF_3$ and $-SO_2-C_{1-6}$-alkyl,

R^9 is hydrogen or C_{1-6}-alkyl,

D is aryl or heteroaryl,

which may optionally be substituted with one or more substituents selected from

- halogen, $-CF_3$, $-OCF_3$, $-SCF_3$, $-CN$, $-NO_2$, C_{1-10}-alkyl, C_{2-6}-alkenyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, amino, C_{1-6}-alkylamino, di-C_{1-6}-alkylamino, $-SO_2CF_3$ and $-SO_2-C_{1-6}$-alkyl,

- C_{3-8}-cycloalkyl, C_{3-8}-cycloalkenyl, aryl and aryl-C_{1-6}-alkoxy,

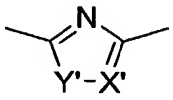
wherein the non-aromatic and aromatic rings optionally may be substituted with one to three substituents selected from halogen, $-CF_3$, $-OCF_3$, $-SCF_3$, $-CN$, $-NO_2$, C_{1-10}-alkyl, C_{2-6}-alkenyl, C_{1-6}-alkoxy and C_{1-6}-alkylthio, or with two substituents on adjacent positions which are combined to form a bridge $-O-(CH_2)_m-O-(CH_2)_p-$ or $-O-(CF_2)_m-O-(CF_2)_p-$, wherein m is an integer of from 1 to 6, and p is 0 or 1,

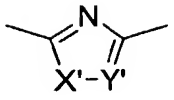
- or with two substituents on adjacent positions which are combined to form a bridge $-O-(CH_2)_m-O-(CH_2)_p-$ or $-O-(CF_2)_m-O-(CF_2)_p-$, wherein m is an integer of from 1 to 6, and p is 0 or 1,

or a substituent on B may be combined with a substiuent on D to form a –C(=O)- bridge,

as well as any diastereomer or enantiomer or tautomeric form thereof including mixtures of these.

4. A compound according to claim 3, wherein B is

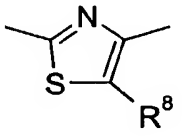


or


,

wherein X' and Y' are as defined in claim 3.

5. A compound according to claim 4, wherein B is



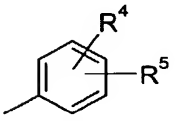
,

wherein R^8 is as defined in claim 3.

6. A compound according to claims 3-5, wherein E is

C_{1-10}-alkyl,

C_{3-10}-cycloalkyl, which may optionally be substituted as defined in claim 3,



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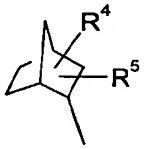

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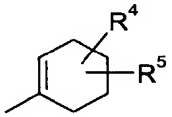

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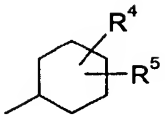

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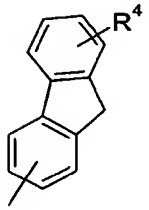

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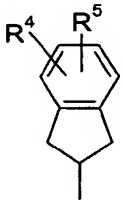
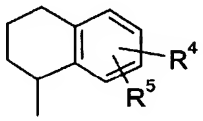
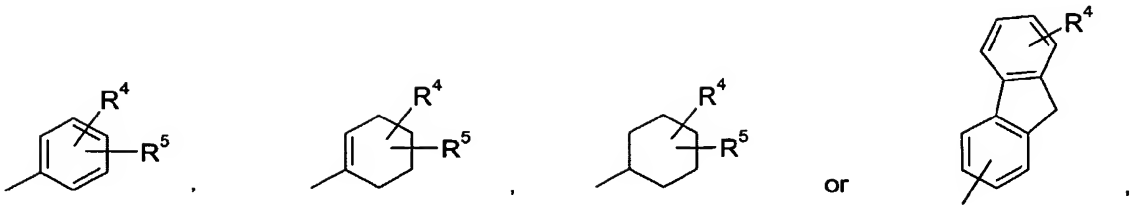


or


,

wherein R^4 and R^5 are as defined in claim 3.

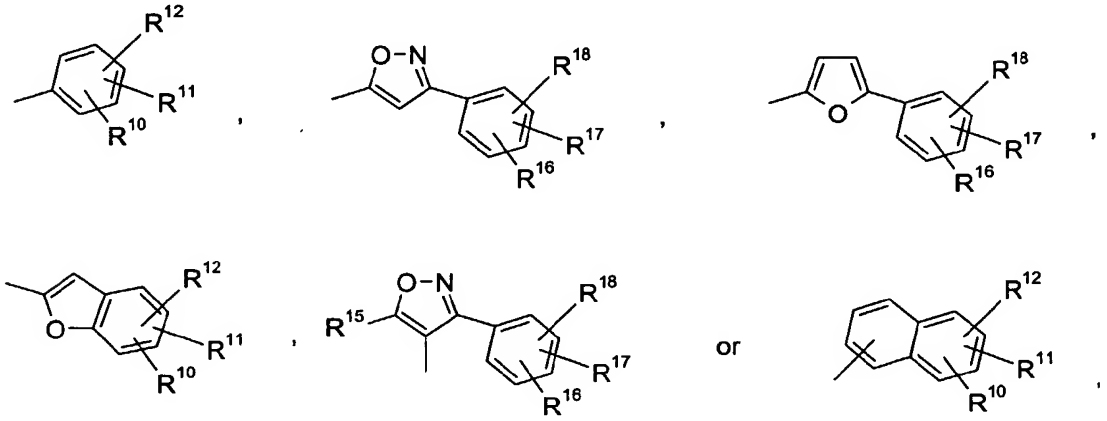
7. A compound according to claim 6 wherein E is



wherein R^4 is hydrogen and R^5 is C_{1-6}-alkyl, C_{1-6}-alkoxy, cyclohexyl, halogen, $-CF_3$ or cyclohex-1-enyl,

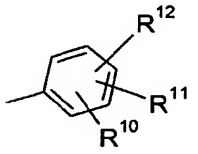
or R^4 and R^5 on adjacent positions may be combined to form a bridge C_{1-6}-alkylene.

8. A compound according to claims 3-7, wherein D is



wherein R^{10}, R^{11}, R^{12}, R^{15}, R^{16}, R^{17} and R^{18} are as defined in claim 3.

9. A compound according to claim 8, wherein D is



wherein R^{10}, R^{11} and R^{12} are as defined in claim 3.

10. A compound according to claim 8 or 9, wherein R^{10}, R^{11} and R^{12} independently are hydrogen, halogen, $-OCF_3$, $-CF_3$, $-NO_2$, di-C_{1-6}-alkylamino, C_{1-10}-alkyl, C_{1-6}-alkoxy or -CN,

phenyl or phenyl-C_{1-6}-alkoxy,

or two of R^{10}, R^{11} and R^{12} in adjacent positions form a bridge $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$ or $-O-CH_2-CH_2-CH_2-O-$.

11. A compound of claim 10 wherein one of R^{10}, R^{11} and R^{12} represent hydrogen.

12. A compound according to claim 11, wherein one or two of R^{10}, R^{11} and R^{12} is hydrogen, and the remaining is independently selected from halogen, $-OCF_3$, $-CF_3$, $-NO_2$, di-C_{1-6}-alkylamino, C_{1-10}-alkyl, C_{1-6}-alkoxy or –CN.

13. A compound according to any one of the previous claims 3-12, wherein the compounds is selected from

3-(4-{[[4-(4-Chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)amino]methyl}benzoylamino)-propionic acid,

3-(4-{[[4-(3,4-Dichlorophenyl)thiazol-2-yl]-(5,6,7,8-tetrahydronaphthalen-2-yl)amino]methyl}-benzoylamino)propionic acid

3-[4-({(4-Chlorophenyl)-[4-(4-trifluoromethoxyphenyl)thiazol-2-yl]amino}methyl)benzoyl-amino]propionic acid,

3-[4-({(4-Chlorophenyl)-[4-(4-trifluoromethylphenyl)thiazol-2-yl]amino}methyl)benzoylamino]-propionic acid or

3-[4-({(4-Trifluoromethoxyphenyl)-[4-(4-trifluoromethylphenyl)thiazol-2-yl]amino}methyl)-benzoylamino]propionic acid,

14. The composition according to any one of claims 1-13, comprising

3-(4-{[[4-(3,4-Dichlorophenyl)thiazol-2-yl]-(5,6,7,8-tetrahydronaphthalen-2-yl)amino]methyl}-benzoylamino)propionic acid as a salt with tert-butylamine.

15. The composition according to any one of claims 1-13 comprising

3-(4-{[[4-(4-chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)amino]methyl}benzoylamino)-propionic acid as a salt with L-lysine.

16. The composition according to any one of claims 1-13, comprising

3-(4-{[[4-(4-chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)amino]methyl}benzoylamino)-propionic acid as a salt with L-histidine.

17. The composition according to any one of claims 1-13, comprising

3-(4-{[[4-(4-chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)amino]methyl}benzoylamino)-propionic acid as a salt with monoethanolamine.

18. The composition according to any one of claims 1-13, comprising

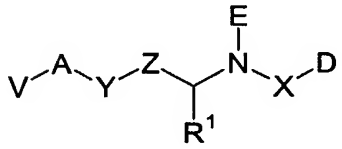
3-(4-{[[4-(4-chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)amino]methyl}benzoylamino)-propionic acid as a salt with tert-butylamine.

19. The composition according to any one of claims 1-13, comprising3-(4-{[[4-chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)amino]methyl}benzoylamino)propionic acid as a salt with 1,2-ethylenediamine.

20. The composition according to any one of claims 1-13, comprising

3-(4-{[[4-(4-chlorophenyl)thiazol-2-yl]-(4-trifluoromethylphenyl)amino]methyl}benzoylamino)-propionic acid as a salt with N,N'-dibenzylethylenediamine.

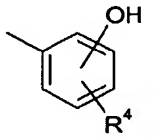
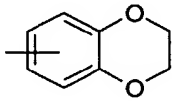
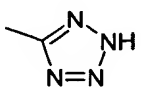
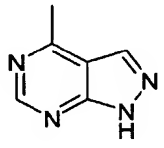
21. A composition according to claims 1-2 comprising a compound represented by the general formula (I):



(I)

wherein

V is $-C(O)OR^2$, $-C(O)NR^2R^3$, $-C(O)NR^2OR^3$, $-S(O)_2OR^2$,




or


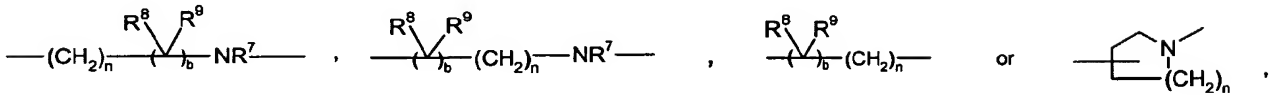
wherein

R^2 and R^3 independently are hydrogen or C_{1-6}-alkyl,

R^4 is hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^5$, $-NR^5R^6$ or C_{1-6}-alkyl,

wherein R^5 and R^6 independently are hydrogen or C_{1-6}-alkyl,

A is



wherein

b is 0 or 1,

n is 0, 1, 2 or 3,

R^7 is hydrogen, C_{1-6}-alkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,

R^8 and R^9 independently are hydrogen or C_{1-6}-alkyl,

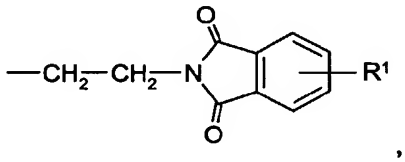
Y is -C(O)-, $-S(O)_2$-, -O- or a valence bond,

Z is phenylene or a divalent radical derived from a 5 or 6 membered heteroaromatic ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur,

which may optionally be substituted with one or two groups R^{46} and R^{47} selected from hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{10}$, $-NR^{10}R^{11}$ and C_{1-6}-alkyl,

wherein R^{10} and R^{11} independently are hydrogen or C_{1-6}-alkyl,

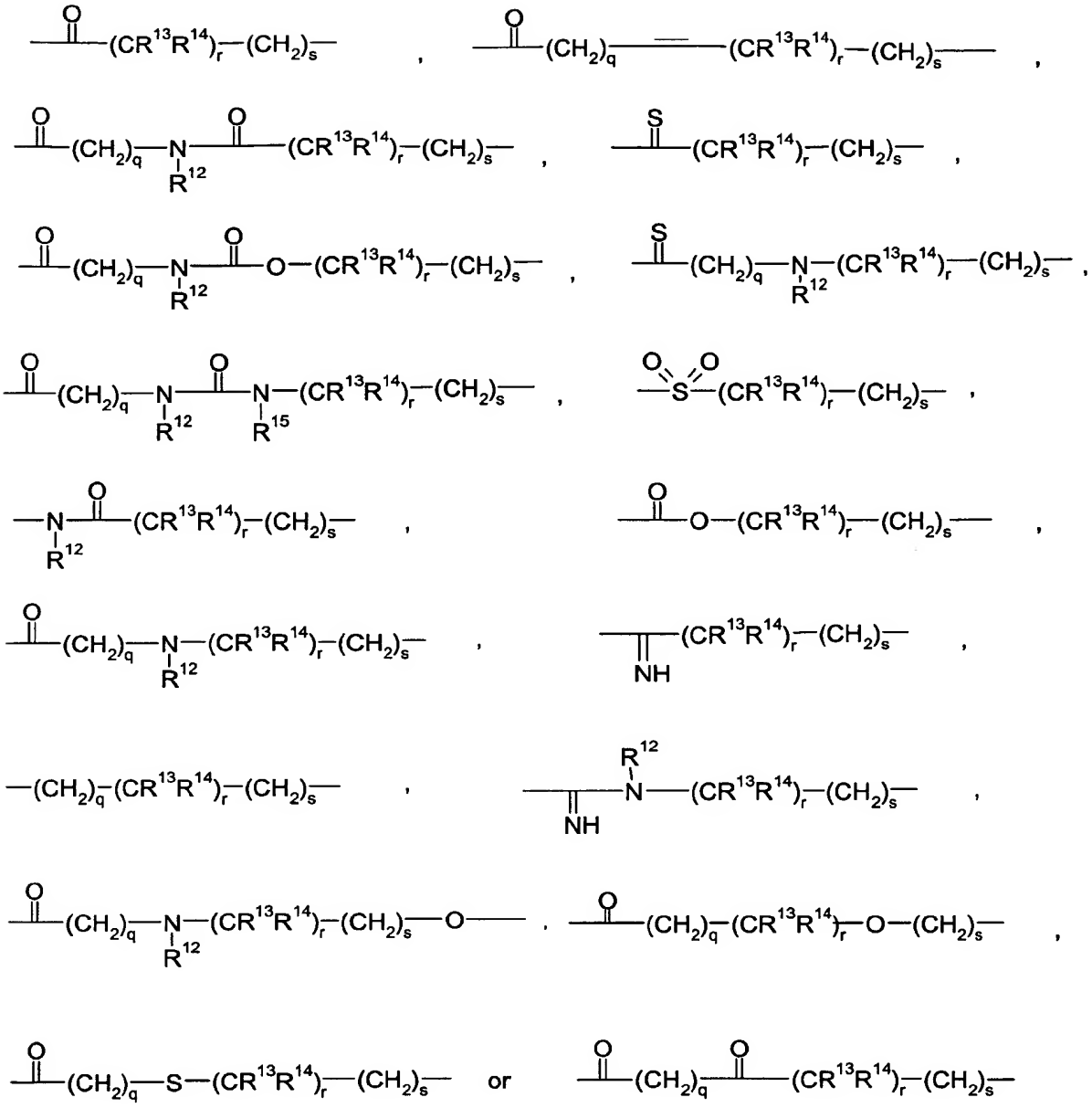
or -A-Y-Z- together are



,

R^1 is hydrogen or C_{1-6}-alkyl,

X is



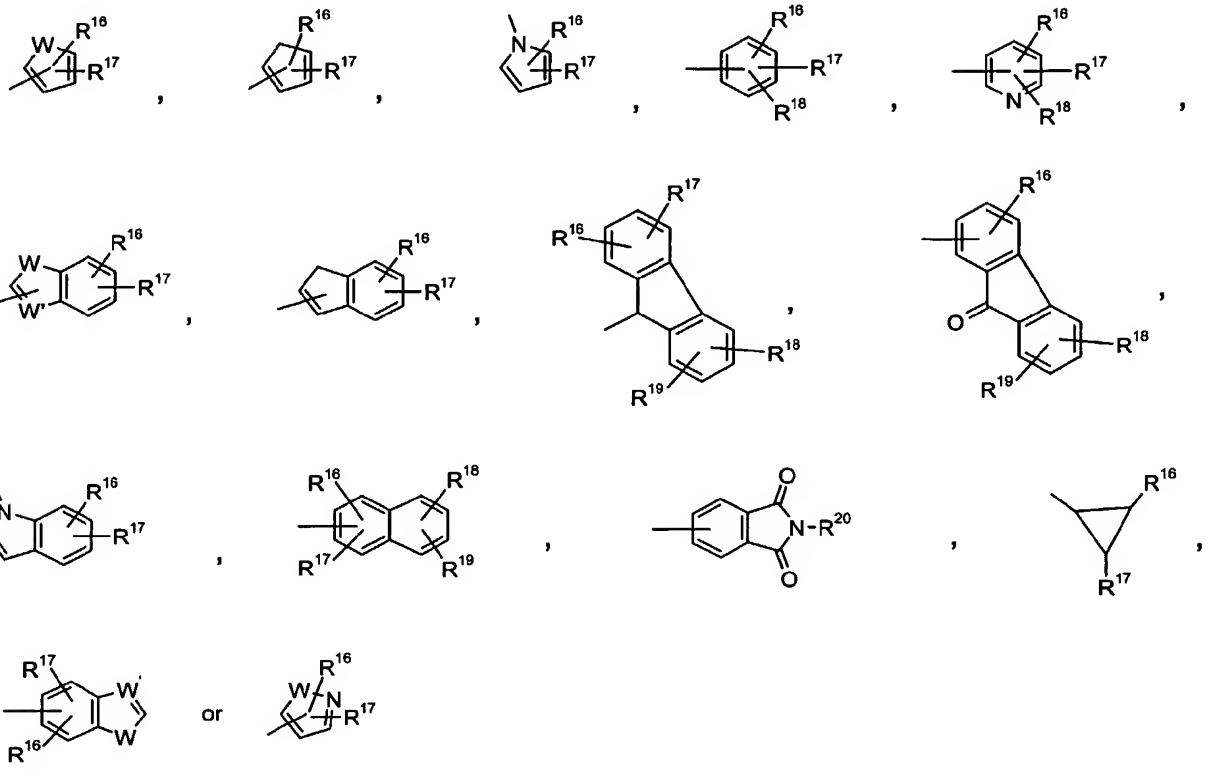
wherein

r is 0 or 1,

q and s independently are 0, 1, 2 or 3,

R^{12}, R^{13}, R^{14} and R^{15} independently are hydrogen or C_{1-6}-alkyl,

D is



wherein

W is -O-, -S-, -$S(O)_2$- or -NR^{20}-,

W' is =$CR^{20'}$- or =N-,

R^{16}, R^{17}, R^{18} and R^{19} independently are

- hydrogen, halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$OS(O)_2CF_3$, -SCF_3, -NO_2, -OR^{21}, -$NR^{21}R^{22}$, -SR^{21}, -$NR^{21}S(O)_2R^{22}$, -$S(O)_2NR^{21}R^{22}$,

$-S(O)NR^{21}R^{22}$, $-S(O)R^{21}$, $-S(O)_2R^{21}$, $-OS(O)_2R^{21}$, $-C(O)NR^{21}R^{22}$, $-OC(O)NR^{21}R^{22}$, $-NR^{21}C(O)R^{22}$, $-CH_2C(O)NR^{21}R^{22}$, $-OCH_2C(O)NR^{21}R^{22}$, $-CH_2OR^{21}$, $-CH_2NR^{21}R^{22}$, $-OC(O)R^{21}$, $-C(O)R^{21}$ or $-C(O)OR^{21}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{21}$, $-NR^{21}R^{22}$, $-SR^{21}$, $-S(O)R^{21}$, $-S(O)_2R^{21}$, $-C(O)NR^{21}R^{22}$, $-OC(O)NR^{21}R^{22}$, $-NR^{21}C(O)R^{22}$, $-OCH_2C(O)NR^{21}R^{22}$, $-C(O)R^{21}$ and $-C(O)OR^{21}$,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkoxy, C_{3-8}-cycloalkyloxy, C_{3-8}-cycloalkyl-C_{1-6}-alkylthio, C_{3-8}-cycloalkylthio, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl or heterocyclyl-C_{2-6}-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from

$-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{21}$, $-NR^{21}R^{22}$, $-SR^{21}$, $-S(O)R^{21}$, $-S(O)_2R^{21}$, $-C(O)NR^{21}R^{22}$, $-OC(O)NR^{21}R^{22}$, $-NR^{21}C(O)R^{22}$, $-OCH_2C(O)NR^{21}R^{22}$, $-C(O)R^{21}$ and $-C(O)OR^{21}$,

C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{21}$, $-NR^{21}R^{22}$, $-SR^{21}$, $-S(O)R^{21}$, $-S(O)_2R^{21}$, $-C(O)NR^{21}R^{22}$, $-OC(O)NR^{21}R^{22}$, $-NR^{21}C(O)R^{22}$, $-OCH_2C(O)NR^{21}R^{22}$, $-C(O)R^{21}$ and $-C(O)OR^{21}$,

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from

halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$OS(O)_2CF_3$, -SCF_3, -NO_2, -OR^{21}, -$NR^{21}R^{22}$, -SR^{21}, -$NR^{21}S(O)_2R^{22}$, -$S(O)_2NR^{21}R^{22}$, -$S(O)NR^{21}R^{22}$, -$S(O)R^{21}$, -$S(O)_2R^{21}$, -$OS(O)_2R^{21}$, -$C(O)NR^{21}R^{22}$, -$OC(O)NR^{21}R^{22}$, -$NR^{21}C(O)R^{22}$, -$CH_2C(O)NR^{21}R^{22}$, -$OCH_2C(O)NR^{21}R^{22}$, -CH_2OR^{21}, -$CH_2NR^{21}R^{22}$, -$OC(O)R^{21}$, -$C(O)R^{21}$ and -$C(O)OR^{21}$,

C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -SCF_3, -OR^{21}, -$NR^{21}R^{22}$, -SR^{21}, -$S(O)R^{21}$, -$S(O)_2R^{21}$, -$C(O)NR^{21}R^{22}$, -$OC(O)NR^{21}R^{22}$, -$NR^{21}C(O)R^{22}$, -$OCH_2C(O)NR^{21}R^{22}$, -$C(O)R^{21}$ and -$C(O)OR^{21}$,

wherein R^{21} and R^{22} independently are hydrogen, -CF_3, C_{1-6}-alkyl, tri-C_{1-6}-alkylsilyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, aryl, aryl-C_{1-6}-alkyl or heteroaryl,

or R^{21} and R^{22} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{16} to R^{19} when placed in adjacent positions together may form a bridge $-(CR^{16'}R^{17'})_a$-O-$(CR^{18'}R^{19'})_c$-O-,

wherein

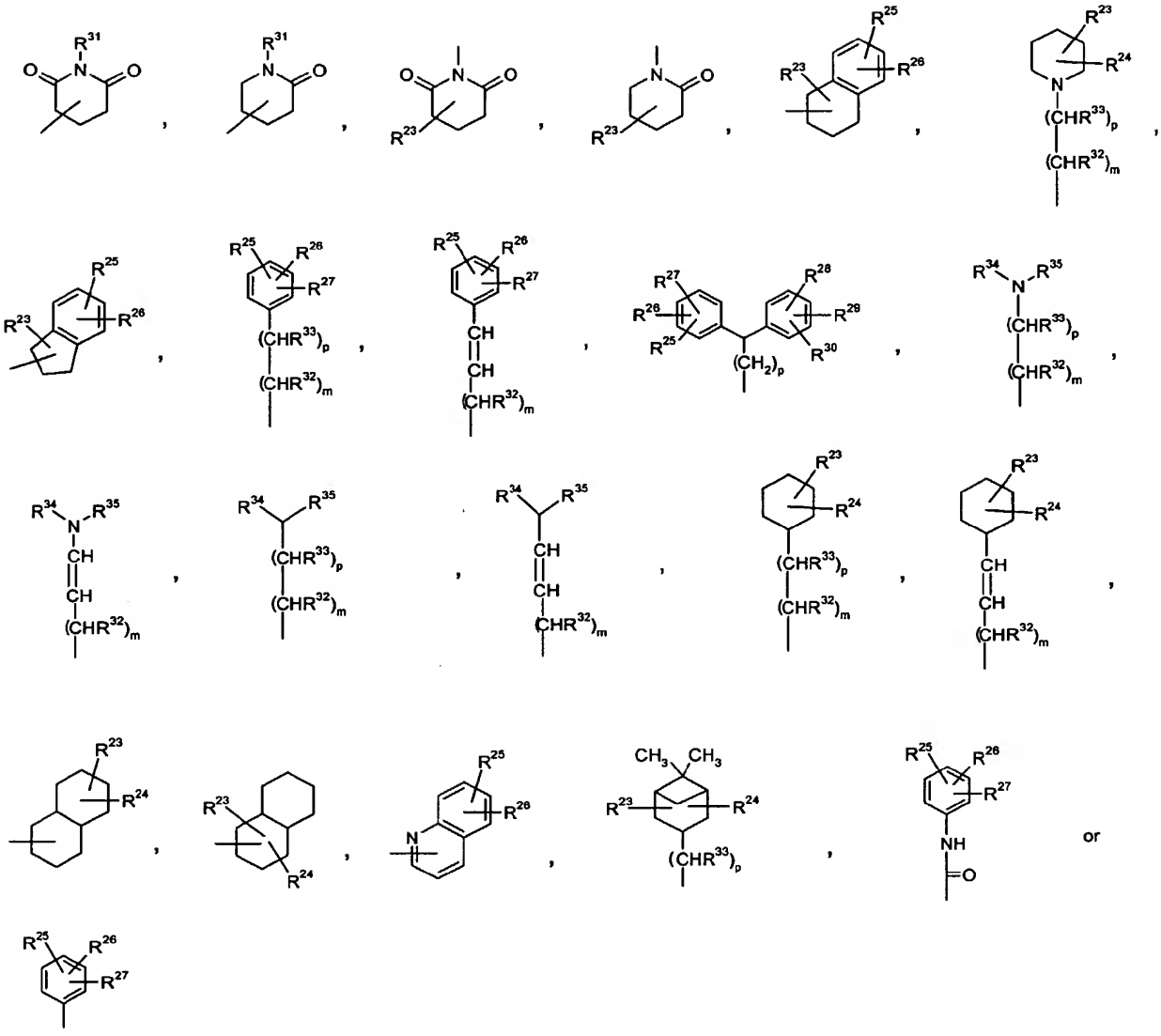
a is 0, 1 or 2,

c is 1 or 2,

$R^{16'}$, $R^{17'}$, $R^{18'}$ and $R^{19'}$ independently are hydrogen, C_{1-6}-alkyl or halogen,

R^{20} and $R^{20'}$ independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,

E is a 3 to 9 membered mono- or bicyclic ring which may optionally contain one or two double bonds and which may optionally contain one or two heteroatoms selected from nitrogen, oxygen and sulfur, wherein one or two groups R^{23} and R^{24} may be attached to the same or different ring carbon atoms and wherein a group R^{31} may be attached to a ring nitrogen atom when present, or



wherein

m and p independently are 0, 1, 2, 3 or 4, with the proviso that when both m and p are present in the same formula at least one of m and p is different from 0,

R^{23} and R^{24} independently are

- hydrogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{36}$, $-NR^{36}R^{37}$, $-SR^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-C(O)NR^{36}R^{37}$, $-OC(O)NR^{36}R^{37}$, $-NR^{36}C(O)R^{37}$, $-OCH_2C(O)NR^{36}R^{37}$, $-C(O)R^{36}$ or $-C(O)OR^{36}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{36}$, $-NR^{36}R^{37}$, $-SR^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-C(O)NR^{36}R^{37}$, $-OC(O)NR^{36}R^{37}$, $-NR^{36}C(O)R^{37}$, $-OCH_2C(O)NR^{36}R^{37}$, $-C(O)R^{36}$ and $-C(O)OR^{36}$,

- C_{3-8}-cycloalkyl, C_{3-8}-cycloalkylidene, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl or heterocyclyl-C_{2-6}-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from

$-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{36}$, $-NR^{36}R^{37}$, $-SR^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-C(O)NR^{36}R^{37}$, $-OC(O)NR^{36}R^{37}$, $-NR^{36}C(O)R^{37}$, $-OCH_2C(O)NR^{36}R^{37}$, $-C(O)R^{36}$ and $-C(O)OR^{36}$,

C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{36}$, $-NR^{36}R^{37}$, $-SR^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-C(O)NR^{36}R^{37}$, $-OC(O)NR^{36}R^{37}$, $-NR^{36}C(O)R^{37}$, $-OCH_2C(O)NR^{36}R^{37}$, $-C(O)R^{36}$ and $-C(O)OR^{36}$,

- aryl, aryloxy, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from

halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-OS(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{36}$, $-NR^{36}R^{37}$, $-SR^{36}$, $-NR^{36}S(O)_2R^{37}$, $-S(O)_2NR^{36}R^{37}$, $-S(O)NR^{36}R^{37}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-OS(O)_2R^{36}$, $-C(O)NR^{36}R^{37}$, $-OC(O)NR^{36}R^{37}$, $-NR^{36}C(O)R^{37}$, $-CH_2C(O)NR^{36}R^{37}$, $-CH_2C(O)NR^{36}R^{37}$, $-CH_2OR^{36}$, $-CH_2NR^{36}R^{37}$, $-OC(O)R^{36}$, $-C(O)R^{36}$ and $-C(O)OR^{36}$,

C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{36}$, $-NR^{36}R^{37}$, $-SR^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-C(O)NR^{36}R^{37}$, $-OC(O)NR^{36}R^{37}$, $-NR^{36}C(O)R^{37}$, $-OCH_2C(O)NR^{36}R^{37}$, $-C(O)R^{36}$ and $-C(O)OR^{36}$,

wherein R^{36} and R^{37} independently are hydrogen, C_{1-6}-alkyl or aryl,

of which the aryl moiety optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{38}$, $-NR^{38}R^{39}$ and C_{1-6}-alkyl,

wherein R^{38} and R^{39} independently are hydrogen or C_{1-6}-alkyl,

or R^{36} and R^{37} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or R^{23} and R^{24} when attached to the same ring carbon atom or different ring carbon atoms together may form a radical $-O-(CH_2)_t-CR^{40}R^{41}-(CH_2)_l-O-$, $-(CH_2)_t-CR^{40}R^{41}-(CH_2)_l-$ or $-S-(CH_2)_t-CR^{40}R^{41}-(CH_2)_l-S-$,

wherein

t and l independently are 0, 1, 2, 3, 4 or 5,

R^{40} and R^{41} independently are hydrogen or C_{1-6}-alkyl,

R^{25} to R^{30} independently are hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{42}$, $-NR^{42}R^{43}$, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl,

wherein R^{42} and R^{43} independently are hydrogen or C_{1-6}-alkyl, or

R^{42} and R^{43} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

R^{31}, R^{32} and R^{33} independently are hydrogen or C_{1-6}-alkyl,

R^{34} and R^{35} independently are

- hydrogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkanoyl, $-C(O)NR^{44}R^{45}$ or $-S(O)_2R^{45}$,

- aryl, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkanoyl or aryl-C_{1-6}-alkyl,

of which the aryl moieties optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{44}$, $-NR^{44}R^{45}$ and C_{1-6}-alkyl,

wherein R^{44} and R^{45} independently are hydrogen or C_{1-6}-alkyl, or

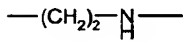
R^{34} and R^{35} when attached to a carbon atom together with the said carbon atom may form a 3 to 8 membered cyclic ring optionally containing one or two heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds, or

R^{34} and R^{35} when attached to a nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds,

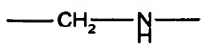
as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these.

22. A compound according to claim 21, wherein V is -C(O)OH or 5-tetrazolyl.

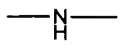
23. A compound according to claim 21 or 22, wherein A is



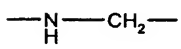
or



or



or

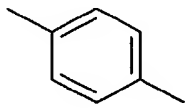


24. A compound according to any one of the claims 21-23, wherein Y is -C(O)-,

or Y is a valence bond.

25. A compound according to any one of the claims 21 to 24,

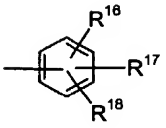
wherein Z is



26. A compound according to claims 21-25, wherein R^1 is hydrogen or methyl.

27. A compound according to claims 21-26, wherein X is -C(O)NH-, -C(O)NHCH$_2$-, -C(O)NHCH(CH$_3$)-, -C(O)NHCH$_2$CH$_2$-, -C(O)CH$_2$-, -CH$_2$-, -C(O)- or -NHC(O)-.

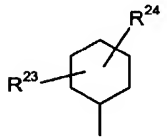
28. A compound according to claims 23-27, wherein D is



wherein one or two of R^{16}, R^{17}, and R^{18} are hydrogen and the remaining is independently selected from -OCF_3, -SCF_3 -CF_3, –$S(O)_2CH_3$, phenyl, halogen, C_{1-6}-alkyl, nitro, -S-C_{1-6}-alkyl or -$S(O)_2NR^{21}R^{22}$, wherein R^{21} is C_{1-6}-alkyl and R^{22} is phenyl.

29. A compound according to claim

21-28, wherein E is

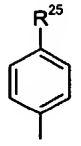


,

wherein R^{23} is hydrogen and R^{24} is C_{1-6}-alkyl such as *tert*-butyl or C_{3-8}-cycloalkyl such as cyclohexyl, wherein R^{23} and R^{24} are both C_{1-6}-alkyl or wherein R^{23} and R^{24} together form the radical –$(CH_2)_5$-.

30. A compound according to claims

21-28, wherein E is



,

wherein R^{25} is –OCF_3, -CF_3, C_{1-6}-alkyl such as *tert*-butyl, phenyl, piperidyl, C_{3-8}-cycloalkyl such as cyclohexyl or C_{4-8}-cycloalkenyl such as cyclohexenyl.

31. The compound according to any one of the claims

21-30 wherein the compound is any of the following

3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-propionic acid,

4-[3-(3,5-Bistrifluoromethylphenyl)-1-(4-tert-butylcyclohexyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide,

(S)-4-[3-[1-(4-Chlorophenyl)ethyl]-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide,

4-[1-(4-Cyclohexylphenyl)-3-(3-fluoro-5-trifluoromethylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

4-[3-(3-Bromo-5-trifluoromethylphenyl)-1-(4-*tert*-butylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide,

4-[3-(3-Bromo-5-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide,

4-[3-(3-Bromophenyl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide.

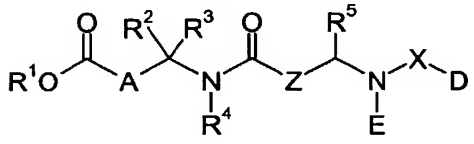
32. The composition according to any one of the claims 1-2 and

21-31 comprising N-[4-({4-(1-cyclohexen-1-yl)[(3,5-dichloroanilino)carbonyl]anilino}methyl)benzoyl]-β-alanine and tert-butylamine.

33. The composition according to any one of the claims 1-2 and

21-31 comprising N-[4-({4-(1-cyclohexen-1-yl)[(3,5-dichloroanilino)carbonyl]anilino}methyl)benzoyl]-β-alanine and L-arginine.

34. A composition according to claims 1-2 comprising a compound represented by the general formula (I):



(I)

wherein

R^1, R^2, R^3, R^4 and R^5 independently are hydrogen or C_{1-6}-alkyl,

A is -C(O)-, -CH(OR^6)- or –CHF-,

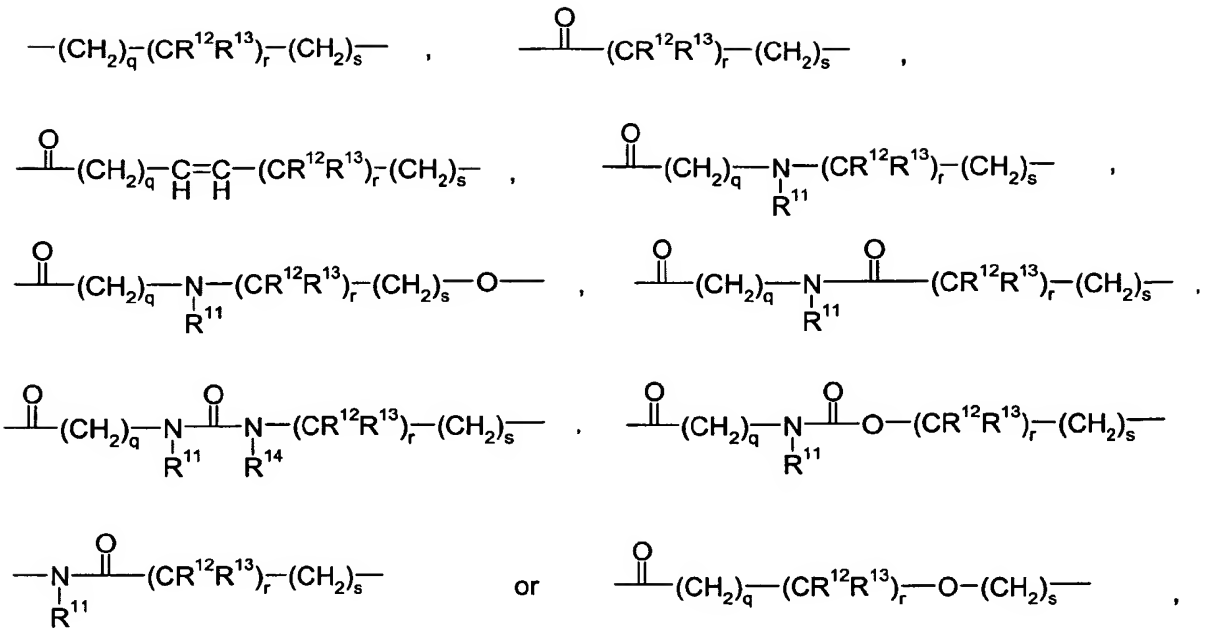
wherein R^6 is hydrogen or C_{1-6}-alkyl,

Z is arylene or a divalent radical derived from a 5 or 6 membered heteroaromatic ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur,

which may optionally be substituted with one or two groups R^7 and R^8 selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^9$, $-NR^9R^{10}$ and C_{1-6}-alkyl,

wherein R^9 and R^{10} independently are hydrogen or C_{1-6}-alkyl,

X is



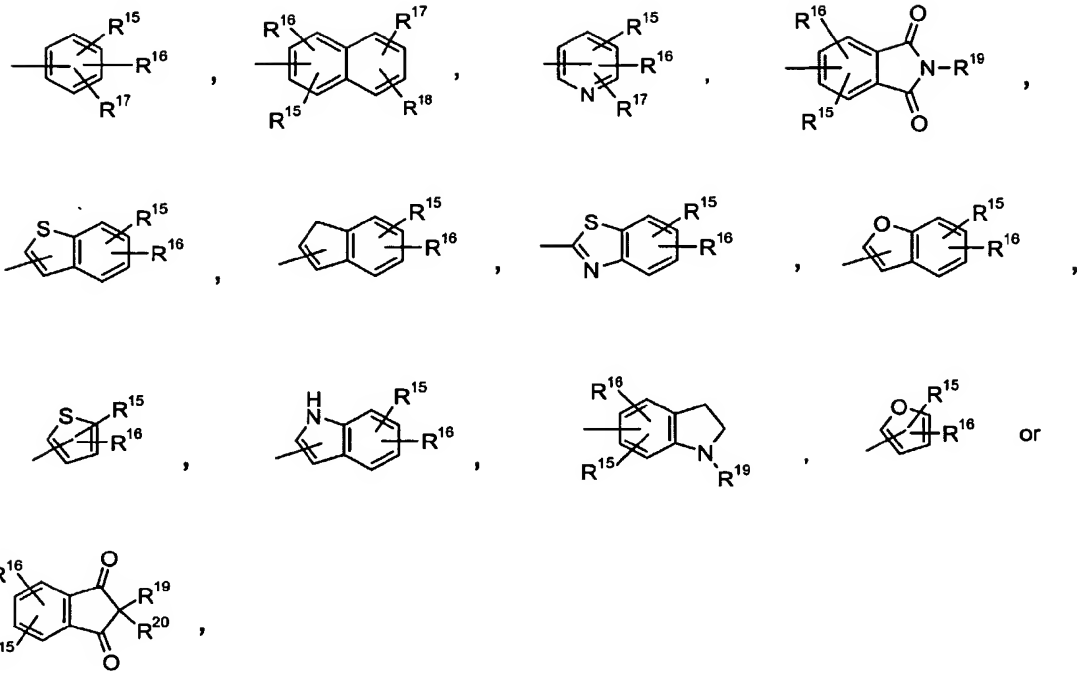
wherein

r is 0 or 1,

q and s independently are 0, 1, 2 or 3,

R^{11}, R^{12}, R^{13} and R^{14} independently are hydrogen, C_{1-6}-alkyl or C_{3-8}-cycloalkyl,

D is



wherein

R^{15}, R^{16}, R^{17} and R^{18} independently are

- hydrogen, halogen, -CN, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{21}$, $-NR^{21}R^{22}$, $-SR^{21}$, $-NR^{21}S(O)_2R^{22}$, $-S(O)_2NR^{21}R^{22}$, $-S(O)NR^{21}R^{22}$, $-S(O)R^{21}$, $-S(O)_2R^{21}$, $-C(O)NR^{21}R^{22}$, $-OC(O)NR^{21}R^{22}$, $-NR^{21}C(O)R^{22}$, $-CH_2C(O)NR^{21}R^{22}$, $-OCH_2C(O)NR^{21}R^{22}$, $-OC(O)R^{21}$, $-C(O)R^{21}$ or $-C(O)OR^{21}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{21}$, $-NR^{21}R^{22}$ and C_{1-6}-alkyl,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkoxy, C_{3-8}-cycloalkyloxy, C_{3-8}-cycloalkyl-C_{1-6}-alkylthio, C_{3-8}-cycloalkylthio, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, $-C(O)OR^{21}$, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{21}$, $-NR^{21}R^{22}$ and C_{1-6}-alkyl,

wherein R^{21} and R^{22} independently are hydrogen, C_{1-6}-alkyl, aryl-C_{1-6}-alkyl or aryl,

or R^{21} and R^{22} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{15} to R^{18} when placed in adjacent positions together may form a bridge $-(CR^{23}R^{24})_a-O-(CR^{25}R^{26})_c-O-$,

wherein

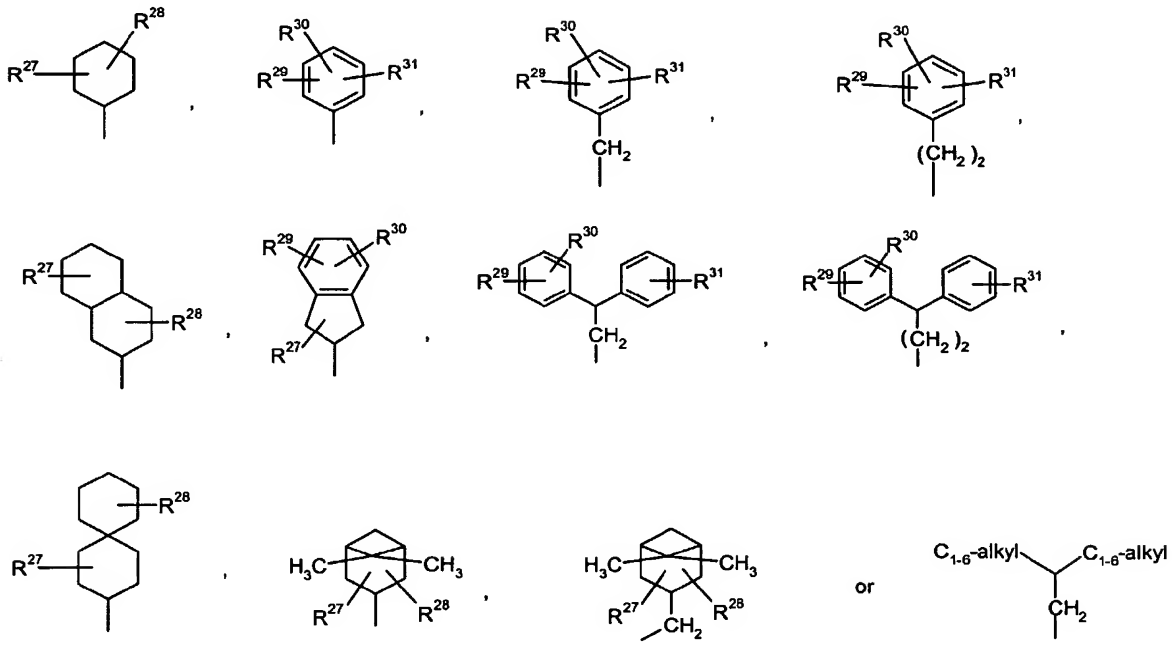
a is 0, 1 or 2,

c is 1 or 2,

R^{23}, R^{24}, R^{25} and R^{26} independently are hydrogen, C_{1-6}-alkyl or fluorine,

R^{19} and R^{20} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,

E is



wherein

R^{27} and R^{28} independently are

hydrogen, halogen, -CN, $-CF_3$, $-OR^{32}$, $-NR^{32}R^{33}$, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl or aryl,

wherein the aryl group optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{32}$, $-NR^{32}R^{33}$ and C_{1-6}-alkyl,

wherein R^{32} and R^{33} independently are hydrogen or C_{1-6}-alkyl, or

R^{32} and R^{33} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

R^{29}, R^{30} and R^{31} independently are

- hydrogen, halogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{34}$, $-NR^{34}R^{35}$, $-SR^{34}$, $-S(O)R^{34}$, $-S(O)_2R^{34}$, $-C(O)NR^{34}R^{35}$, $-OC(O)NR^{34}R^{35}$, $-NR^{34}C(O)R^{35}$, $-OCH_2C(O)NR^{34}R^{35}$, $-C(O)R^{34}$ or $-C(O)OR^{34}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{34}$, $-NR^{34}R^{35}$ and C_{1-6}-alkyl,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{34}$, $-NR^{34}R^{35}$ and C_{1-6}-alkyl,

wherein R^{34} and R^{35} independently are hydrogen, C_{1-6}-alkyl or aryl,

or R^{34} and R^{35} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{29}, R^{30} and R^{31} when attached to the same ring carbon atom or different ring carbon atoms together may form a radical $-O-(CH_2)_t-CR^{36}R^{37}-(CH_2)_l-O-$, $-(CH_2)_t-CR^{36}R^{37}-(CH_2)_l-$ or $-S-(CH_2)_t-CR^{36}R^{37}-(CH_2)_l-S-$,

wherein

t and l independently are 0, 1, 2, 3, 4 or 5,

R^{36} and R^{37} independently are hydrogen or C_{1-6}-alkyl,

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these.

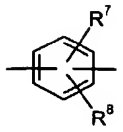
35. A compound according to claim 34, wherein R^1, R^2, R^3, R^4 and R^5 are hydrogen.

36. A compound according to claim 34 or 35, wherein A is –CHF-.

37. A compound according to claim 34 or 35, wherein A is $-CH(OR^6)-$, wherein R^6 is as defined in claim 34.

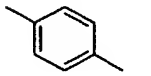
38. A compound according to claim 37, wherein A is –CH(OH)-.

39. A compound according to any of the claims 34-38, wherein Z is



wherein R^7 and R^8 are as defined in claim 34.

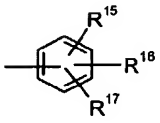
40. A compound according to claim 39, wherein Z is



41. A compound according to claims 34-40, wherein X is -C(O)NH-, -C(O)NHCH$_2$-, -C(O)NHCH(CH$_3$)-, -C(O)CH$_2$- or -C(O)-.

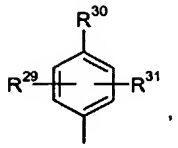
42. A compound according to claim 41, wherein X is -C(O)NH-.

43. A compound according to claims 34-42, wherein D is



wherein R^{15}, R^{16} and R^{17} independently are hydrogen, halogen, -CN, -CF$_3$, -OCF$_3$ or C$_{1-6}$-alkoxy.

44. A compound according to claims 34-43, wherein E is



wherein R^{29} and R^{31} are both hydrogen, and R^{30} is cyclohexenyl,

- which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{34}$, $-NR^{34}R^{35}$ and C_{1-6}-alkyl,

- wherein R^{34} and R^{35} independently are hydrogen, C_{1-6}-alkyl or aryl,

- or R^{34} and R^{35} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds.

45. A compound according to claim 44, wherein R^{29}, R^{30} and R^{31} independently are hydrogen, C_{1-6}-alkyl, phenyl, C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl.

46. A compound according to claim 45, wherein R^{29} and R^{31} are both hydrogen and R^{30} is C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl

47. A compound according to any one of the claims 34-46 wherein the compound is selected from the following:

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(3-methoxy-5-trifluoromethylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[3-(3,5-Bis(trifluoromethyl)phenyl)-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[3-(3-Bromophenyl)-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(3-trifluoromethylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(3-fluoro-5-trifluoromethylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[3-(3-Cyano-5-trifluoromethylphenyl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[3-(3-Cyano-5-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[3-(3-Bromo-5-trifluoromethylphenyl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3-methoxy-5-trifluoromethylphenyl)ureidomethyl]-benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[3-(3-Bromophenyl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[3-(3-Bromo-5-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(S)-*Trans*-3-{4-[3-(3,5-Bis(trifluoromethyl)phenyl)-1-(4-*tert*-butylcyclohexyl)ureidomethyl]-benzoylamino}-2-hydroxypropionic acid

(R)-*Trans*-3-{4-[3-(3,5-bis(trifluoromethyl)phenyl)-1-(4-*tert*-butylcyclohexyl)ureidomethyl]-benzoylamino}-2-hydroxypropionic acid

Trans-(R)-3-{4-[3-(3-methyl-5-trifluoromethylphenyl)-1-(4-*tert*-butylcyclohexyl)ureidomethyl]-benzoylamino}-2-hydroxypropionic acid

(RS)-3-{4-[1-(4-*tert*-Butylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(RS)-3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(S)-3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[3-(3-Chlorophenyl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-phenylureidomethyl]benzoylamino}-2-hydroxy-propionic acid

(R)-3-{4-[3-Benzyl-1-(4-cyclohex-1-enylphenyl)ureidomethyl]benzoylamino}-2-hydroxy-propionic acid

(RS)-3-{4-[1-(4-Cyclohex-1-enylphenyl)3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2-fluoropropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]benzoyl-amino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexen-1-ylphenyl)-3-(3-methanesulfonyl-4-trifluoromethoxyphenyl)-ureidomethyl]benzoylamino}-2-hydroxypropionic acid

Trans-(R)-3-{4-[-3-(3,5-bis(methyl)phenyl)-1-(4-*tert*-butylcyclohexyl)ureidomethyl]benzoyl-amino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-(3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3-fluoro-5-trifluoromethylphenyl)ureidomethyl]-benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(3-methylsulfanylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(2,2,4,4-tetrafluoro-4*H*-benzo[1,3]dioxin-6-yl)ureido-methyl]benzoylamino}-2-hydroxypropionic acid

3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2(R)-methoxypropionic acid:

3-(4-{3-(3,5-Dichlorophenyl)-1-[4-(2-methylcyclohex-1-enyl)phenyl]ureidomethyl}benzoyl-amino)-2-(R)-hydroxypropionic acid and (R,S)-3-(4-{3-(3,5-dichlorophenyl)-1-[4-(6-methylcyclohex-1-enyl)phenyl]ureidomethyl}benzoylamino)-2-(R)-hydroxypropionic acid

3-{4-[1-[4-(4-*tert*-Butylcyclohex-1-enyl)phenyl]-3-(3,5-dichlorophenyl)ureidomethyl]benzoyl-amino}-2-(R)-hydroxypropionic acid

(R,S)-3-(4-(3-(3,5-dichlorophenyl)-1-(4-(3-methylcyclohex-1-enyl)phenyl)ureidomethyl)benzoylamino)-2-hydroxypropionic acid

3-{4-[3-[1(*S*)-(4-Chlorophenyl)ethyl]-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}-2(*R*)-hydroxypropionic acid

3-{4-[3-Biphenyl-2-ylmethyl-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}-2(*R*)-hydroxypropionic acid

(R)-3-{4-[3-(4-Cyano-3-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[3-(3-*tert*-Butylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(3-hydroxymethyl-4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-*tert*-Butylphenyl)-3-(3,4-dichlorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,4-dichlorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(3,4-dichlorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(2,2,4,4-tetrafluoro-4*H*-benzo[1,3]dioxin-6-yl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-*tert*-Butylphenyl)-3-(2,2,4,4-tetrafluoro-4*H*-benzo[1,3]dioxin-6-yl)ureidomethyl]-benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(2,2,4,4-tetrafluoro-4*H*-benzo[1,3]dioxin-6-yl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-*tert*-Butylphenyl)-3-(3,4-difluorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(3,4-difluorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,4-difluorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(4-fluoro-3-nitrophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(4-isopropylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,4-dichlorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-{4-[3-(4-Acetylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

3-{4-[3-[1(RS)-(4-Bromophenyl)ethyl]-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}-2(R)-hydroxypropionic acid

(R)-3-{4-[1-(4-Cyclohexylphenyl)-3-(3,5-difluorophenyl)ureidomethyl]benzoylamino}-2-hydroxypropionic acid

(R)-3-[4-({(4-*tert*-Butylcyclohexyl)-[2-(4-trifluoromethoxyphenyl)acetyl]amino}methyl)benzoylamino]-2-hydroxypropionic acid

(R)-3-[4-({(4-*tert*-Butylcyclohexyl)-[2-(3-fluoro-5-trifluoromethylphenyl)acetyl]amino}methyl)-benzoylamino]-2-hydroxypropionic acid

(R)-3-[4-({(2,2-Diphenylethyl)-[2-(3-fluoro-5-trifluoromethylphenyl)acetyl]amino}methyl)-benzoylamino]-2-hydroxypropionic acid

(R)-3-(4-{[(5-Chlorobenzo[*b*]thiophene-3-carbonyl)-(2,2-diphenylethyl)amino]methyl}benzoylamino)-2-hydroxypropionic acid

(R)-3-[4-({(2,2-Diphenylethyl)-[2-(4-trifluoromethoxyphenyl)acetyl]amino}methyl)benzoylamino]-2-hydroxypropionic acid

(R)-3-(4-{[(4-*tert*-Butylcyclohexyl)-(5-chlorobenzo[*b*]thiophene-3-carbonyl)amino]methyl}-benzoylamino)-2-hydroxypropionic acid

(R)-3-(4-{[(2,2-Diphenylethyl)-(5-trifluoromethoxy-1*H*-indole-2-carbonyl)amino]methyl}-benzoylamino)-2-hydroxypropionic acid

(R)-3-[4-({(4-Cyclohexylphenyl)-[(4-trifluoromethoxyphenyl)acetyl]amino}methyl)benzoylamino]-2-hydroxypropionic acid

(R)-3-[4-({(4-Cyclohexylphenyl)-[(3-trifluoromethoxyphenyl)acetyl]amino}methyl)benzoyl-amino]-2-hydroxypropionic acid

(R)-3-[4-({(4-Cyclohexylphenyl)-[(3-fluoro-5-trifluoromethylphenyl)acetyl]amino}methyl)-benzoylamino]-2-hydroxypropionic acid

(R)-3-(4-{([(3,5-Bis(trifluoromethyl)phenyl)acetyl]-(4-cyclohexylphenyl)amino)methyl}benzoyl-amino)-2-hydroxypropionic acid

(R)-3-[4-({(4-Cyclohexylphenyl)-[(3-trifluoromethylphenyl)acetyl]amino}methyl)benzoylamino]-2-hydroxypropionic acid

(R)-3-[4-({(4-Cyclohexylphenyl)-[(3,4-dichlorophenyl)acetyl]amino}methyl)benzoylamino]-2-hydroxypropionic acid

(R)-3-(4-{[[(3-Bromophenyl)acetyl]-(4-cyclohexylphenyl)amino]methyl}benzoylamino)-2-hydroxypropionic acid

(R)-3-(4-{[(Biphenyl-4-ylacetyl)-(4-cyclohexylphenyl)amino]methyl}benzoylamino)-2-hydroxy-propionic acid

(R)-3-(4-{[(4-Cyclohexylphenyl)-(2-naphthylacetyl)amino]methyl}benzoylamino)-2-hydroxy-propionic acid

(R)-3-(4-{[(3-(3,5-Bis(trifluoromethyl)phenyl)propionyl)-(4-cyclohexylphenyl)amino]methyl}-benzoylamino)-2-hydroxypropionic acid

(R)-3-[4-({(4-Cyclohexylphenyl)-[3-(3-nitrophenyl)propionyl]amino}methyl)benzoylamino]-2-hydroxypropionic acid

(2R)-N-[4-({4-cyclohexyl[(3,5-dichloroanilino)carbonyl]anilino}methyl)benzoyl]-2-hydroxy-β-alanine (2R)-N-[4-({[1,1'-biphenyl]-4-yl[(3,5-dichloroanilino)carbonyl]amino}methyl)benzoyl]-2-hydroxy-β-alanine.

48. The composition according to any one of the claims 1-2 and 34-47, comprising

(R)-[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2R-hydroxypropionic acid as a tert-butylamine salt.

49. The composition according to any one of the claims 1-2 and 34-47, comprising

(R)-[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2R-hydroxypropionic acid as an L-arginine salt.

50. The composition according to any one of the claims 1-2 and 34-47, comprising (R)-[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2R-hydroxypropionic acid as a salt with N,N'-dibenzylethylenediamine.

51. The composition according to claim 50 comprising (R)-[3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2R-hydroxypropionic acid as a salt with N,N'-dibenzylethylenediamine as a 2:1 ratio between compound and N,N'-dibenzylethylenediamine.

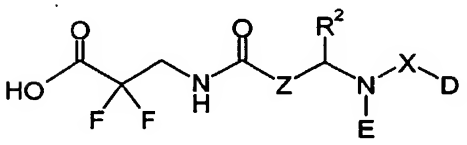
52. The composition according to any one of the claims 1-2 and 34-47 comprising (2R)-N-[4-({[1,1'-biphenyl]-4-yl[(3,5-dichloroanilino)carbonyl]amino}methyl)benzoyl]-2-hydroxy-β-alanine and benzathine.

53. The composition according to claim 52 comprising (2R)-N-[4-({[1,1'-biphenyl]-4-yl[(3,5-dichloroanilino)carbonyl]amino}methyl)benzoyl]-2-hydroxy-β-alanine and benzathine as a 2:1 ratio between compound and N,N'-dibenzylethylenediamine.

54. The composition according to any one of the claims 1-2 and 34-47 comprising ((2R)-N-[4-({4-cyclohexyl[(3,5-dichloroanilino)carbonyl]anilino}methyl)benzoyl]-2-hydroxy-β-alanine as a salt with N,N'-dibenzylethylenediamine.

55. The composition according to claim 54 comprising ((2R)-N-[4-({4-cyclohexyl[(3,5-dichloroanilino)carbonyl]anilino}methyl)benzoyl]-2-hydroxy-β-alanine as a salt with N,N'-dibenzylethylenediamine in a 2:1 ratio of compound to N,N'-dibenzylethylenediamine.

56. A composition according to claims 1-2 comprising a compound represented by the general formula (I):



(I)

wherein

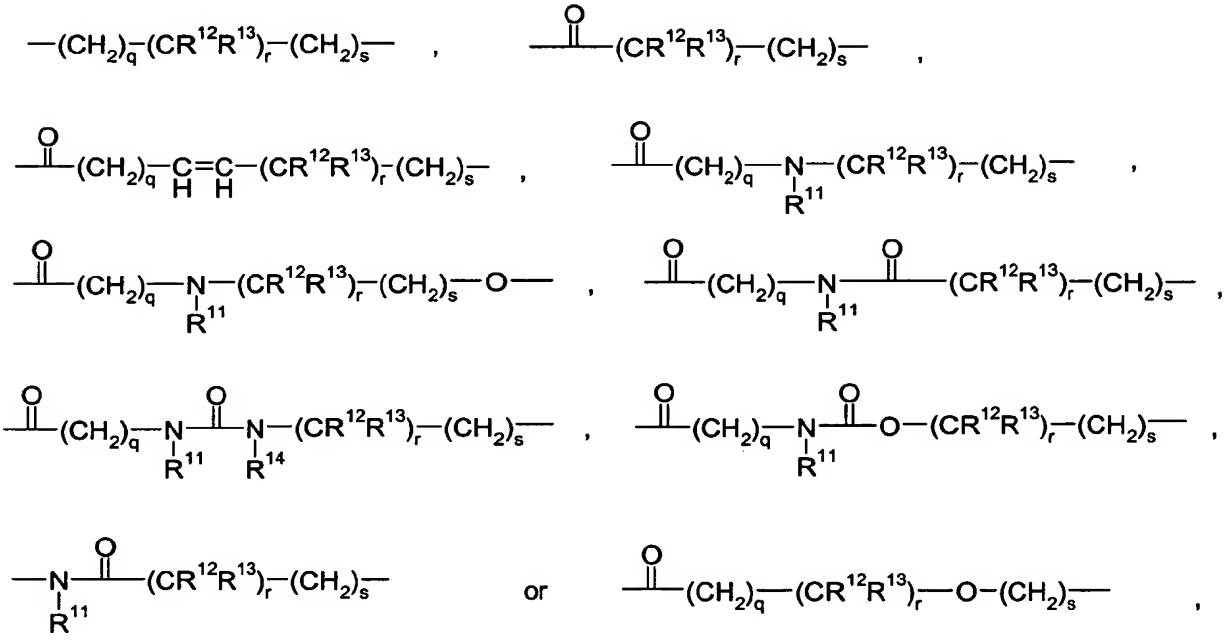
R^2 is hydrogen or C_{1-6}-alkyl,

Z is arylene or a divalent radical derived from a 5 or 6 membered heteroaromatic ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur,

which may optionally be substituted with one or two groups R^7 and R^8 selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^9$, $-NR^9R^{10}$ and C_{1-6}-alkyl,

wherein R^9 and R^{10} independently are hydrogen or C_{1-6}-alkyl,

X is



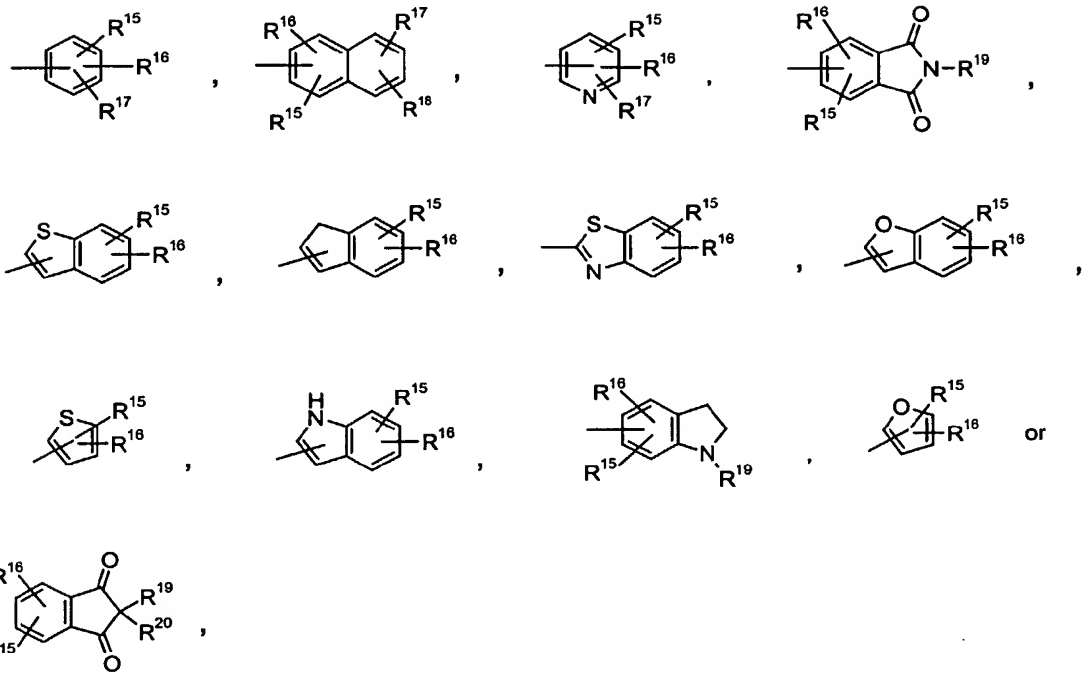
wherein

r is 0 or 1,

q and s independently are 0, 1, 2 or 3,

R^{11}, R^{12}, R^{13} and R^{14} independently are hydrogen or C_{1-6}-alkyl,

D is



wherein

R^{15}, R^{16}, R^{17} and R^{18} independently are

- hydrogen, halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$S(O)_2CF_3$, -SCF_3, -NO_2, -OR^{21}, -$NR^{21}R^{22}$, -SR^{21}, -$NR^{21}S(O)_2R^{22}$, -$S(O)_2NR^{21}R^{22}$, -$S(O)NR^{21}R^{22}$, -$S(O)R^{21}$, -$S(O)_2R^{21}$, -$C(O)NR^{21}R^{22}$, -$OC(O)NR^{21}R^{22}$, -$NR^{21}C(O)R^{22}$, -$CH_2C(O)NR^{21}R^{22}$, -$OCH_2C(O)NR^{21}R^{22}$, -CH_2OR^{21}, -$CH_2NR^{21}R^{22}$, -$OC(O)R^{21}$, -$C(O)R^{21}$ or -$C(O)OR^{21}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{21}$, $-NR^{21}R^{22}$ and C_{1-6}-alkyl,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkoxy, C_{3-8}-cycloalkyloxy, C_{3-8}-cycloalkyl-C_{1-6}-alkylthio, C_{3-8}-cycloalkylthio, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{21}$, $-NR^{21}R^{22}$ and C_{1-6}-alkyl,

wherein R^{21} and R^{22} independently are hydrogen, C_{1-6}-alkyl or aryl,

or R^{21} and R^{22} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{15} to R^{18} when placed in adjacent positions together may form a bridge $-(CR^{23}R^{24})_a$-O-$(CR^{25}R^{26})_c$-O-,

wherein

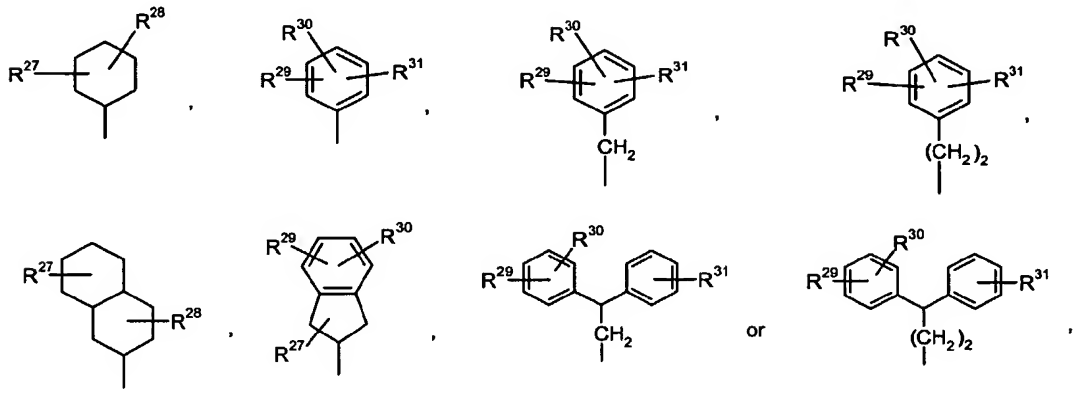
a is 0, 1 or 2,

c is 1 or 2,

R^{23}, R^{24}, R^{25} and R^{26} independently are hydrogen, C_{1-6}-alkyl or fluorine,

R^{19} and R^{20} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,

E is



wherein

R^{27} and R^{28} independently are

hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{32}$, $-NR^{32}R^{33}$, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl or aryl,

wherein the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{32}$, $-NR^{32}R^{33}$ and C_{1-6}-alkyl,

wherein

R^{32} and R^{33} independently are hydrogen or C_{1-6}-alkyl, or

R^{32} and R^{33} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

R^{29}, R^{30} and R^{31} independently are

- hydrogen, halogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{34}$, $-NR^{34}R^{35}$, $-SR^{34}$, $-S(O)R^{34}$, $-S(O)_2R^{34}$, $-C(O)NR^{34}R^{35}$, $-OC(O)NR^{34}R^{35}$, $-NR^{34}C(O)R^{35}$, $-OCH_2C(O)NR^{34}R^{35}$, $-C(O)R^{34}$ or $-C(O)OR^{34}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{34}$, $-NR^{34}R^{35}$ and C_{1-6}-alkyl,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{34}$, $-NR^{34}R^{35}$ and C_{1-6}-alkyl,

wherein R^{34} and R^{35} independently are hydrogen, C_{1-6}-alkyl or aryl,

or R^{34} and R^{35} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{29}, R^{30} and R^{31} when attached to the same ring carbon atom or different ring carbon atoms together may form a radical $-O-(CH_2)_t-CR^{36}R^{37}-(CH_2)_l-O-$, $-(CH_2)_t-CR^{36}R^{37}-(CH_2)_l-$ or $-S-(CH_2)_t-CR^{36}R^{37}-(CH_2)_l-S-$,

wherein

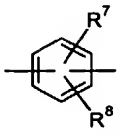
t and l independently are 0, 1, 2, 3, 4 or 5,

R^{36} and R^{37} independently are hydrogen or C_{1-6}-alkyl,

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these.

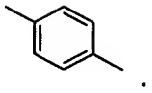
57. A compound according to claim 56, wherein R^2 is hydrogen.

58. A compound according to any of the claims 56 or 57, wherein Z is

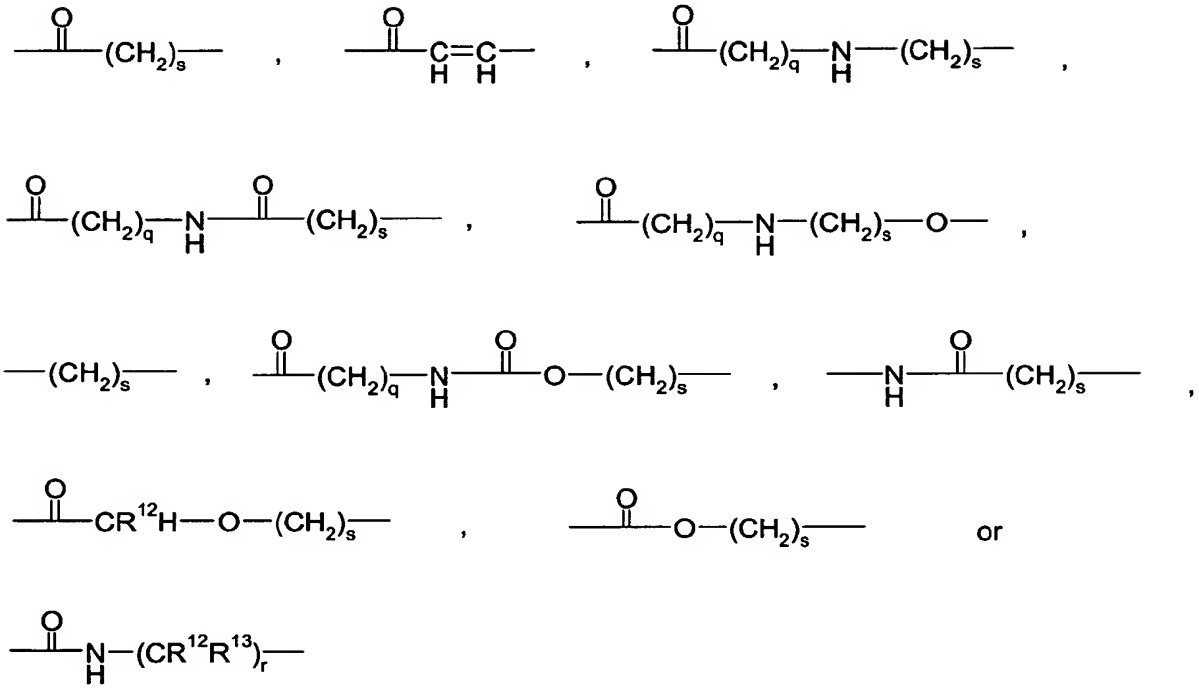


wherein R^7 and R^8 are as defined in claim 56.

59. A compound according to claim 58, wherein Z is

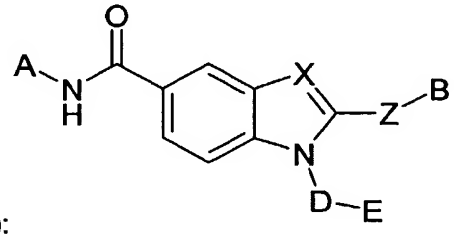


60. A compound according to claims 56-59, wherein X is



wherein q is 0 or 1, r is 0 or 1, s is 0, 1 or 2, and R^{12} and R^{13} independently are hydrogen or C_{1-6}-alkyl.

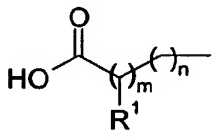
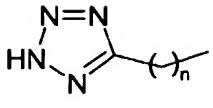
61. A composition according to claims 1-2 comprising a compound represented by the general formula (I):



(I)

wherein

A is


or

,

m is 0 or 1,

n is 0, 1, 2 or 3,

with the proviso that m and n must not both be 0,

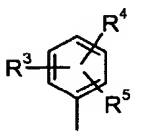
R^1 is hydrogen, fluoro or $-(CH_2)_o-OR^2$,

o is 0 or 1,

R^2 is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkanoyl, aryl or aryl-C_{1-6}-alkyl,

X is –N= or –CH=,

B is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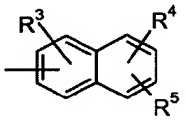
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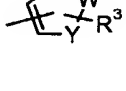
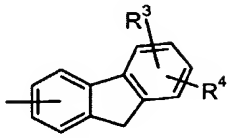
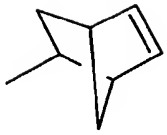

,

or


V and W independently are –CH= or –N=,

Y is –O-, –S- or –NH-,

R^3, R^4 and R^5 independently are

- hydrogen, halogen, -CN, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^6$, $-NR^6R^7$, $-SR^6$, $-NR^6S(O)_2R^7$, $-S(O)_2NR^6R^7$, $-S(O)NR^6R^7$, $-S(O)R^6$, $-S(O)_2R^6$, $-C(O)NR^6R^7$, $-OC(O)NR^6R^7$, $-NR^6C(O)R^7$, $-CH_2C(O)NR^6R^7$, $-OCH_2C(O)NR^6R^7$, $-OCH_2C(O)OR^6$, $-OC(O)R^6$, $-C(O)R^6$ or $-C(O)OR^6$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from fluoro, -CN, $-CF_3$, $-OCF_3$, $-OR^6$ and $-NR^6R^7$,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkoxy, C_{3-8}-cycloalkyloxy, C_{3-8}-cycloalkyl-C_{1-6}-alkylthio, C_{3-8}-cycloalkylthio, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl,

of which the cyclic moieties may optionally be substituted with one or more substituents selected from fluoro, $-C(O)OR^6$, -CN, $-CF_3$, $-OCF_3$, $-OR^7$, $-NR^6R^7$ and C_{1-6}-alkyl,

- aryl, arylthio, aryl-C_{1-6}-alkylthio, aryloxy, aryloxycarbonyl, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

of which the cyclic moieties may optionally be substituted with one or more substituents selected from halogen, -C(O)OR^6, -CN, -CF_3, -OCF_3, -NO_2, -OR^7, -NR^{8}R^7 and C_{1-6}-alkyl,

R^6 and R^7 independently are hydrogen or C_{1-6}-alkyl,

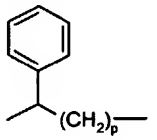
or R^6 and R^7 when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^3 to R^5 when placed in adjacent positions together may form a bridge -$(CR^8R^9)_s$-O-$(CR^{10}R^{11})_t$-O-,

s is 0, 1 or 2,

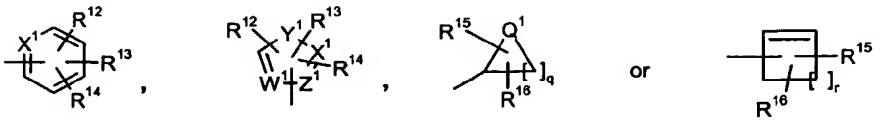
t is 1 or 2,

R^8, R^9, R^{10} and R^{11} independently are hydrogen, C_{1-6}-alkyl or fluoro,

D is –$(CH_2)_p$-,  or –$(CH_2)_p$-O-,

p is 0, 1, 2, 3 or 4,

E is



X^1, Z^1 and W^1 independently are –CH= or –N=,

Y^1 is –O-, –S- or –NH-,

Q^1 is $–CH_2-$ or –NH-,

q is 2, 3, 4, 5 or 6,

r is 1, 2, 3, 4 or 5,

R^{12}, R^{13} and R^{14} independently are

- hydrogen, halogen, -CN, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{17}$, $-NR^{17}R^{18}$, $-SR^{17}$, $-NR^{17}S(O)_2R^{18}$, $-S(O)_2NR^{17}R^{18}$, $-S(O)NR^{17}R^{18}$, $-S(O)R^{17}$, $-S(O)_2R^{17}$, $-C(O)NR^{17}R^{18}$, $-OC(O)NR^{17}R^{18}$, $-NR^{17}C(O)R^{18}$, $-CH_2C(O)NR^{17}R^{18}$, $-OCH_2C(O)NR^{17}R^{18}$, $-OC(O)R^{17}$, $-C(O)R^{17}$ or $-C(O)OR^{17}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from fluoro, -CN, $-CF_3$, $-OCF_3$, $-OR^{17}$ and $-NR^{17}R^{18}$,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkoxy, C_{3-8}-cycloalkyloxy, C_{3-8}-cycloalkyl-C_{1-6}-alkylthio, C_{3-8}-cycloalkylthio, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl,

C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl,

of which the cyclic moieties may optionally be substituted with one or more substituents selected from fluoro, -C(O)OR^{17}, -CN, -CF_3, -OCF_3, -OR^{17} and -$NR^{17}R^{18}$,

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

of which the cyclic moieties may optionally be substituted with one or more substituents selected from halogen, -C(O)OR^{17}, -CN, -CF_3, -OCF_3, -NO_2, -OR^{17}, -$NR^{17}R^{18}$ and C_{1-6}-alkyl,

R^{17} and R^{18} independently are hydrogen or C_{1-6}-alkyl,

or R^{17} and R^{18} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{12} to R^{14} when placed in adjacent positions together may form a bridge -$(CR^{19}R^{20})_x$-O-$(CR^{21}R^{22})_y$-O-,

x is 0, 1 or 2,

y is 1 or 2,

R^{19}, R^{20}, R^{21} and R^{22} independently are hydrogen, C_{1-6}-alkyl or fluoro,

R^{15} and R^{16} independently are hydrogen, halogen, -CN, $-CF_3$, $-OR^{23}$, $-NR^{23}R^{24}$, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, aryl or aryl-C_{1-6}-alkyl,

wherein the cyclic moieties may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{23}$, $-NR^{23}R^{24}$ and C_{1-6}-alkyl,

R^{23} and R^{24} independently are hydrogen or C_{1-6}-alkyl, or

R^{23} and R^{24} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or E is

C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{25}$,$-SR^{25}$, $-NR^{25}R^{26}$ and C_{1-6}-alkyl,

R^{25} and R^{26} independently are hydrogen or C_{1-6}-alkyl, or

R^{25} and R^{26} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

Z is $-(CR^{27}R^{28})_v-(O)_w-(CR^{29}R^{30})_z-$,

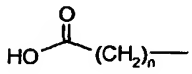
v and z independently are 0, 1 or 2,

w is 0 or 1,

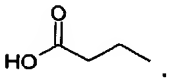
R^{27}, R^{28}, R^{29} and R^{30} independently are hydrogen or C_{1-6}-alkyl,

as well as any diastereomer or enantiomer or tautomeric form thereof including mixtures of these.

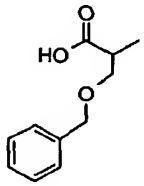
62. A compound according to claim 61, wherein A is


, wherein n is as defined in claim 61.

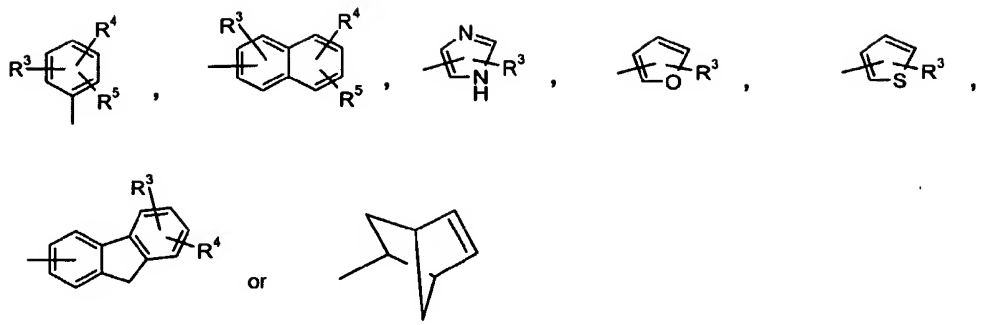
63. A compound according to claim 61, wherein A is


.

64. A compound according to claim 61, wherein A is

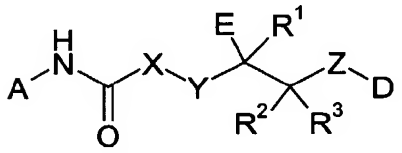

.

65. A compound according to any of the claims 61-64, wherein B is



wherein R^3 to R^5 are as defined in claim 61.

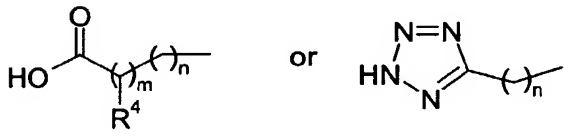
66. A composition according to claims 1-2 comprising a compound represented by the general formula (I):



(I)

wherein

A is



m is 0 or 1,

n is 0, 1, 2 or 3,

with the proviso that m and n must not both be 0,

R^4 is hydrogen, halogen or $-(CH_2)_o-OR^5$,

o is 0 or 1,

R^5 is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkanoyl, aryl or aryl-C_{1-6}-alkyl,

R^1 and R^2 independently are hydrogen, halogen or C_{1-6}-alkyl, or R^1 and R^2 are combined to form a double bond,

R^3 is hydrogen, C_{1-6}-alkyl or halogen, or R^3 and R^2 are combined to form a double bond to oxygen,

X is arylene or heteroarylene, which may optionally be substituted with one or two groups R^6 and R^7 selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-NO_2$, $-OR^8$, $-NR^8R^9$ and C_{1-6}-alkyl,

R^8 and R^9 independently are hydrogen or C_{1-6}-alkyl,

Y is -C(O)-, -O-, $-NR^{10}$-, -S-, -S(O)-, $-S(O)_2$- or $-CR^{11}R^{12}$-,

R^{10} is hydrogen or C_{1-6}-alkyl,

R^{11} and R^{12} independently are hydrogen, C_{1-6}-alkyl or hydroxy, or R^{11} is combined with R^1 to form a double bond, and R^{12} is hydrogen, C_{1-6}-alkyl or hydroxy,

Z is $-C(O)-(CR^{13}R^{14})_p$-, $-O-(CR^{13}R^{14})_p$-, $-S-(CR^{13}R^{14})_p$-, $-S(O)-(CR^{13}R^{14})_p$-, $-S(O)_2-(CR^{13}R^{14})_p$-, $-NR^{15}-(CR^{13}R^{14})_p$- or $-(CR^{13}R^{14})_p$-,

p is 0, 1 or 2,

R^{13} and R^{14} independently are selected from hydrogen, $-CF_3$, $-OCF_3$, $-OCHF_2$ and C_{1-6}-alkyl,

R^{15} is hydrogen or C_{1-6}-alkyl,

D is aryl or heteroaryl, which may optionally be substituted with one or more substituents R^{16}, R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, wherein

R^{16}, R^{17}, R^{18} and R^{19} independently are

- hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{22}$, $-NR^{22}R^{23}$, $-SR^{22}$, $-NR^{22}S(O)_2R^{23}$, $-S(O)_2NR^{22}R^{23}$, $-S(O)NR^{22}R^{23}$, $-S(O)R^{22}$, $-S(O)_2R^{22}$, $-C(O)NR^{22}R^{23}$, $-OC(O)NR^{22}R^{23}$, $-NR^{22}C(O)R^{23}$, $-CH_2C(O)NR^{22}R^{23}$, $-OCH_2C(O)NR^{22}R^{23}$, $-CH_2OR^{22}$, $-CH_2NR^{22}R^{23}$, $-OC(O)R^{22}$, $-C(O)R^{22}$ or $-C(O)OR^{22}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCHF_2$, $-OCF_3$, $-NO_2$, $-OR^{22}$, $-NR^{22}R^{23}$ and C_{1-6}-alkyl,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkoxy, C_{3-8}-cycloalkyloxy, C_{3-8}-cycloalkyl-C_{1-6}-alkylthio, C_{3-8}-cycloalkylthio, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

of which the aromatic and non-aromatic ring systems optionally may be substituted with one or more substituents selected from halogen, $-C(O)OR^{22}$, -CN, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-NO_2$, $-OR^{22}$, $-NR^{22}R^{23}$ and C_{1-6}-alkyl,

R^{22} and R^{23} independently are hydrogen, C_{1-6}-alkyl, aryl-C_{1-6}-alkyl or aryl, or R^{22} and R^{23} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{16} to R^{19} when placed in adjacent positions together may form a bridge $-(CR^{24}R^{25})_a-O-(CR^{26}R^{27})_c-O-$,

a is 0, 1 or 2,

c is 1 or 2,

R^{24}, R^{25}, R^{26} and R^{27} independently are hydrogen, C_{1-6}-alkyl or fluoro,

R^{20} and R^{21} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,

E is

C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl, which may optionally be substituted with one or two substituents R^{28} and R^{29}, which are independently selected from

- hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OR^{33}$, $-NR^{33}R^{34}$, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heteroaryl and aryl,

wherein the heteroaryl and aryl groups optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-NO_2$, $-OR^{33}$, $-NR^{33}R^{34}$ and C_{1-6}-alkyl,

R^{33} and R^{34} independently are hydrogen or C_{1-6}-alkyl,

or R^{33} and R^{34} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

aryl, heteroaryl, aryl-C_{2-6}-alkenyl or aryl-C_{2-6}-alkynyl, of which the aryl and heteroaryl moieties may optionally be substituted with one or more substitutents R^{28}, R^{29}, R^{30}, R^{31} and R^{32},

wherein R^{28} and R^{29} are as defined above, and R^{30}, R^{31} and R^{32} are independently selected from

- hydrogen, halogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{35}$, $-NR^{35}R^{36}$, $-SR^{35}$, $-S(O)R^{35}$, $-S(O)_2R^{35}$, $-C(O)NR^{35}R^{36}$, $-OC(O)NR^{35}R^{36}$, $-NR^{35}C(O)R^{36}$, $-OCH_2C(O)NR^{35}R^{36}$, $-C(O)R^{35}$ and $-C(O)OR^{35}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aroyl, aryl-C_{1-6}-alkoxy, aryl-

C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl and heteroaryl-C_{2-6}-alkynyl,

of which the aromatic and non-aromatic ring systems optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,

wherein R^{35} and R^{36} independently are hydrogen, C_{1-6}-alkyl or aryl,

or R^{35} and R^{36} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

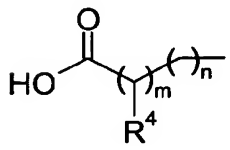
or two of the substituents R^{30}, R^{31} and R^{32} when attached to the same ring carbon atom or adjacent ring carbon atoms together may form a bridge $-O-(CH_2)_t-CR^{37}R^{38}-(CH_2)_l-O-$, $-(CH_2)_t-CR^{37}R^{38}-(CH_2)_l-$ or $-S-(CH_2)_t-CR^{37}R^{38}-(CH_2)_l-S-$,

t and l independently are 0, 1, 2, 3, 4 or 5,

R^{37} and R^{38} independently are hydrogen or C_{1-6}-alkyl,

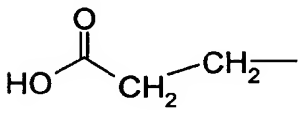
as well as any diastereomer or enantiomer or tautomeric form thereof including mixtures of these.

67. A compound according to claim 66, wherein A is

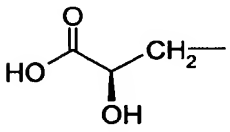


wherein m, n and R^4 are as defined in claim 66.

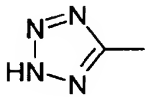
68. A compound according to claim 66, wherein A is



69. A compound according to claim 66, wherein A is

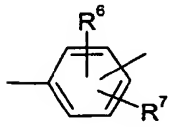


70. A compound according to claim 66, wherein A is



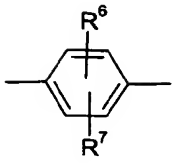
71. A compound according to any of the claims 66-70, wherein X is monocyclic arylene or heteroarylene, which may optionally be substituted as defined in claim 66.

72. A compound according to any of the claim 71, wherein X is



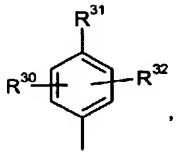
wherein R^6 and R^7 are as defined in claim 66.

73. A compound according to claim 72, wherein X is



wherein R^6 and R^7 are as defined in claim 66.

74. A compound according to claims 66-73 wherein E is



wherein R^{30}, R^{31} and R^{32} are as defined in claim 66.

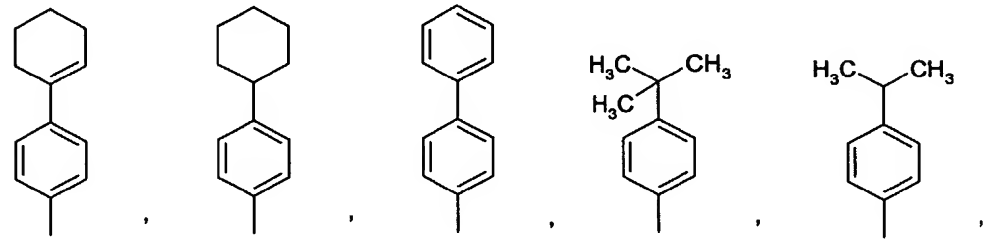
75. A compound according to claim 74, wherein R^{30}, R^{31} and R^{32} independently are

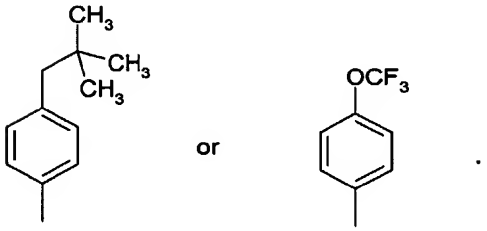
- hydrogen,
- halogen, $-OCF_3$, $-OCHF_2$ or $-SCF_3$,
- C_{1-6}-alkyl, which may optionally be substituted with one or more substituents selected from fluoro, -CN, $-CF_3$, $-OCF_3$, $-OR^{35}$ and $-NR^{35}R^{38}$,
- cyclohexyl or cyclohex-1-enyl, which may optionally be substituted with one or more substituents selected from fluoro, -CN, $-CF_3$, $-OCF_3$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,
- phenyl which may optionally be substituted with one or more substitutents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,

- phenoxy or benzyloxy, of which the phenyl moieties may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,

R^{35} and R^{36} independently are hydrogen or C_{1-6}-alkyl.

76. A compound according to claim 75, wherein E is





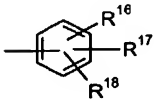
77. A compound according to claims 66-76, wherein R^1 and R^2 are both hydrogen.

78. A compound according to claims 66-76, wherein R^1 and R^2 are combined to form a double bond.

79. A compound according to claims 66-78, wherein R^3 is hydrogen.

80. A compound according to claim 66-79, wherein Z is NH or -C(O)-.

81. A compound according to claim 66-80, wherein D is



wherein R^{16}, R^{17} and R^{18} are as defined in claim 66.

82. A compound according to claim 81, wherein R^{16}, R^{17} and R^{18} independently are

- hydrogen, halogen, $-CF_3$, $-OCF_3$, $-SCF_3$, C_{1-6}-alkyl, C_{1-6}-alkoxy, phenyl, cyclopentyl, cyclohexyl or phenoxy,

- or two of the groups R^{16} to R^{18} when placed in adjacent positions together may form a bridge $-O-(CF_2)_2-O-$, $-CF_2-O-CF_2-O-$ or $-O-CH_2-O-$.

83. A compound according to any one of the claims 66-82 wherein the compound is one of the following:

(Z)-3-{4-[4-Biphenyl-4-yl-2-(4-cyclohexylphenyl)-4-oxobut-2-enoyl]benzoylamino}propionic acid

(Z)-3-{4-[2-Biphenyl-4-yl-4-(4-chlorophenyl)-4-oxobut-2-enoyl]benzoylamino}propionic acid

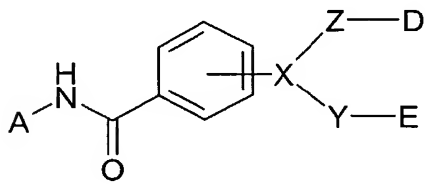
(Z)-3-{4-[4-(4-*tert*-Butylphenyl)-4-oxo-2-(4-trifluoromethoxyphenyl)but-2-enoyl]benzoylamino}-propionic acid

3-{4-[4-(3,5-Bis-trifluoromethylphenyl)-2-(4-cyclohexylphenyl)-4-oxo-butyryl]benzoylamino}-propionic acid

((R)3-{4-[4-(3,5-Bis-trifluoromethylphenyl)-2-(4-cyclohexylphenyl)-4-oxo-butyryl]benzoylamino}-propionic acid

(S)3-{4-[4-(3,5-Bis-trifluoromethylphenyl)-2-(4-cyclohexylphenyl)-4-oxo-butyryl]benzoylamino}-propionic acid

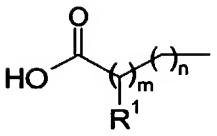
84. A composition according to claims 1-2 comprising a compound represented by the general formula (I):



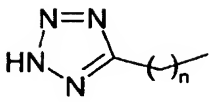
(I)

wherein

A is



or



,

m is 0 or 1,

n is 0, 1, 2 or 3,

with the proviso that m and n must not both be 0,

R^1 is hydrogen, fluoro or $-(CH_2)_o-OR^2$,

o is 0 or 1,

R^2 is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkanoyl , aryl or aryl-C_{1-6}-alkyl,

X is N, CH or C with a double bond to one substituent,

Z is $-CR^3R^4-$, $-(C=O)-(NR^5)-(C_{1-6}\text{-alkyl})_K-$, $-(C=O)-O-(C_{1-6}\text{-alkyl})_K-$, $-(C=O)-(C_{1-6}\text{-alkyl})_K-$, $-(C_{1-6}\text{-alkyl})_K(C=O)-O-$, $-(C=O)-O-(C_{2-6}\text{-alkenyl})_K-$, $-(C=O)-(C_{2-6}\text{-alkenyl})_K-$, $-(C_{1-6}\text{-alkenyl})_K(C=O)-O-$

wherein k is 0 or 1,

R^3, R^4 and R^5 are independently selected from hydrogen, C_{1-6}-alkyl or aryl,

Y is $-(C_{1-6}\text{-alkyl})_s\text{-}(C{=}O)\text{-}(C_{1-6}\text{-alkyl})_t$-, $-(C_{1-6}\text{-alkenyl})_s\text{-}(C{=}O)\text{-}(C_{1-6}\text{-alkyl})_t$-, $-C_{1-6}$-alkyl-, $-C_{2-6}$-alkenyl-, or $-CR^6R^7$-

wherein s and t independently are 0 or 1;

wherein R^6 , R^7 and R^8 independently are selected from hydrogen, C_{1-6}-alkyl and aryl;

D is aryl or heteroaryl, which may optionally be substituted with one or more substituents R^{16}, R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, wherein

R^{16}, R^{17}, R^{18} and R^{19} independently are

- hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{22}$, $-NR^{22}R^{23}$, $-SR^{22}$, $-NR^{22}S(O)_2R^{23}$, $-S(O)_2NR^{22}R^{23}$, $-S(O)NR^{22}R^{23}$, $-S(O)R^{22}$, $-S(O)_2R^{22}$, $-C(O)NR^{22}R^{23}$, $-OC(O)NR^{22}R^{23}$, $-NR^{22}C(O)R^{23}$, $-CH_2C(O)NR^{22}R^{23}$, $-OCH_2C(O)NR^{22}R^{23}$, $-CH_2OR^{22}$, $-CH_2NR^{22}R^{23}$, $-OC(O)R^{22}$, $-C(O)R^{22}$ or $-C(O)OR^{22}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{22}$, $-NR^{22}R^{23}$ and C_{1-6}-alkyl,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkoxy, C_{3-8}-cycloalkyloxy, C_{3-8}-cycloalkyl-C_{1-6}-alkylthio, C_{3-8}-cycloalkylthio, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl,

heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -C(O)OR^{22}, -CN, -CF_3, -OCF_3, -NO_2, -OR^{22}, -$NR^{22}R^{23}$ and C_{1-6}-alkyl,

R^{22} and R^{23} independently are hydrogen, C_{1-6}-alkyl, aryl-C_{1-6}-alkyl or aryl, or R^{22} and R^{23} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{16} to R^{19} when placed in adjacent positions together may form a bridge $-(CR^{24}R^{25})_a$-O-$(CR^{26}R^{27})_c$-O-,

a is 0, 1 or 2,

c is 1 or 2,

R^{24}, R^{25}, R^{26} and R^{27} independently are hydrogen, C_{1-6}-alkyl or fluoro,

R^{20} and R^{21} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,

E is

C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl, which may optionally be substituted with one or two substituents R^{28} and R^{29}, which are independently selected from

- hydrogen, halogen, -CN, -CF_3, -OR^{33}, -$NR^{33}R^{34}$, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heteroaryl and aryl,

wherein the heteroaryl and aryl groups optionally may be substituted with one or more substituents selected from halogen, -CN, -CF_3, -NO_2, -OR^{33}, -$NR^{33}R^{34}$ and C_{1-6}-alkyl,

R^{33} and R^{34} independently are hydrogen or C_{1-6}-alkyl,

or R^{33} and R^{34} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

aryl, heteroaryl, aryl-C_{2-6}-alkenyl or aryl-C_{2-6}-alkynyl, of which the cyclic moieties may optionally be substituted with one to three substitutents R^{30}, R^{31} and R^{32}, which are independently selected from

- hydrogen, halogen, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -SCF_3, -OR^{35}, -$NR^{35}R^{36}$, -SR^{35}, -$S(O)R^{35}$, -$S(O)_2R^{35}$, -$C(O)NR^{35}R^{36}$, -$OC(O)NR^{35}R^{36}$, -$NR^{35}C(O)R^{36}$, -$OCH_2C(O)NR^{35}R^{36}$, -$C(O)R^{35}$ and -$C(O)OR^{35}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from halogen, -CN, -CF_3, -OCF_3, -SCF_3, -NO_2, -OR^{35}, -$NR^{35}R^{36}$ and C_{1-6}-alkyl,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aroyl, aryl-C_{1-6}-alkoxy, aryl-

C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl and heteroaryl-C_{2-6}-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, -CF_3, -OCF_3, -SCF_3, -NO_2, -OR^{35}, -$NR^{35}R^{36}$ and C_{1-6}-alkyl,

wherein R^{35} and R^{36} independently are hydrogen, C_{1-6}-alkyl or aryl,

or R^{35} and R^{36} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

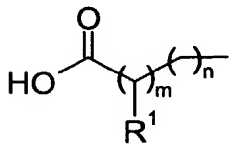
or two of the substituents R^{30}, R^{31} and R^{32} when attached to the same ring carbon atom or different ring carbon atoms together may form a radical -O-$(CH_2)_t$-$CR^{37}R^{38}$-$(CH_2)_l$-O-, -$(CH_2)_t$-$CR^{37}R^{38}$-$(CH_2)_l$- or -S-$(CH_2)_t$-$CR^{37}R^{38}$-$(CH_2)_l$-S-,

t and l independently are 0, 1, 2, 3, 4 or 5,

R^{37} and R^{38} independently are hydrogen or C_{1-6}-alkyl,

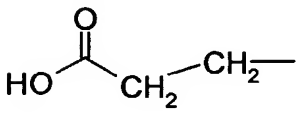
as well as any diastereomer or enantiomer or tautomeric form thereof including mixtures of these.

85. A compound according to claim 84, wherein A is

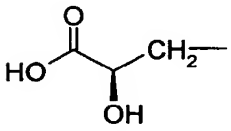


wherein m, n and R^4 are as defined in claim 84.

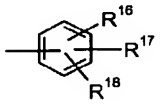
86. A compound according to claim 84, wherein A is



87. A compound according to claim 84, wherein A is



88. A compound according to any one of the preceding claims 84-87, wherein D is

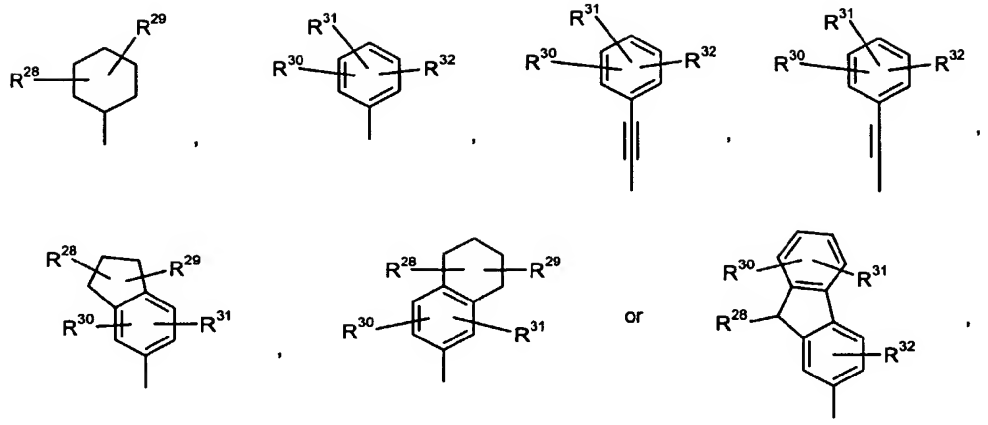


wherein R^{16}, R^{17} and R^{18} independently are

- hydrogen, halogen, CN, $-CF_3$, $-OCF_3$, $-SCF_3$, -S(O) C_{1-6}-alkyl-, -C(O) C_{1-6}-alkyl-, C_{1-6}-alkyl, C_{1-6}-alkoxy, phenyl, cyclopentyl, cyclohexyl or phenoxy,

- or two of the groups R^{16} to R^{18} when placed in adjacent positions together may form a bridge $-O-(CF_2)_2-O-$, $-CF_2-O-CF_2-O-$ or $-O-CH_2-O-$.

89. A compound according to any one of the preceding claims 84-88, wherein E is



wherein R^{28}, R^{29}, R^{30}, R^{31} and R^{32} are independently selected from

- hydrogen,
- halogen, $-OCF_3$, $-OCHF_2$, $-SCF_3$, or $-CF_3$,
- C_{1-6}-alkyl, which may optionally be substituted with one or more substituents selected from fluoro, -CN, $-CF_3$, $-OCF_3$, $-OR^{35}$ and $-NR^{35}R^{36}$,
- cyclohexyl or cyclohex-1-enyl, which may optionally be substituted with one or more substituents selected from fluoro, -CN, $-CF_3$, $-OCF_3$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,
- phenyl which may optionally be substituted with one or more substitutents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,
- phenoxy or benzyloxy, of which the phenyl moieties may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,

- thiadiazolyl,

R^{35} and R^{36} independently are hydrogen or C_{1-6}-alkyl.

90. A compound according to claims 84-89, wherein Y is –C=O-, $–CH_2$-.

91. A compound according to claims 84-90, wherein Z is $–CH_2$-, -(C=O)-(NH), -(C=O)-O - or -(C=O)-CH_2-.

92. The compound according to any one of the preceding claims 84-91, wherein the compound is 3-{4-[(4-Cyclohexylbenzyl)-(4-trifluoromethoxybenzyl)amino]benzoylamino}-propionic acid.

93. The composition according to any one of the preceding claims, wherein the basic counter ion is N,N'-dibenzylethylenediamine (benzathine).

94. The composition according to claim 93, wherein the ratio of compound to counter ion is 2:1;

95. A composition comprising a glucagon antagonist according to any one of the claims 3-94 as a solvate.

96. A composition according to claim 95 wherein the solvate is selected from ethanol, 2-propanol, 2-methyl-1-propanol, n-butanol, 2-butanol, 3-methyl-1-butanol, diethyl ether, *tert*-butyl-methylether, tetrahydrofuran, anisol, acetone, 2-butanon, methylacetate, ethylacetate, n-propylacetate and toluene.

97. A composition according to any of the claims 95-96 comprising 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid in a solvate form.

98. A composition according to claim 97 comprising 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid as a solvate with one of the following solvents ethanol, 2-propanol, 2-methyl-1-propanol, n-butanol, 2-butanol, 3-methyl-1-butanol, diethyl ether, *tert*-butyl-methylether, tetrahydrofuran, anisol, acetone, 2-butanon, methylacetate, ethylacetate, n-propylacetate and toluene.

99. A composition according to any of the claim 98 comprising 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid as a solvate with 2-butanol, 3-methyl-1-butanol and 2-methyl-1-propanol.

100. A composition according to any of the claims 95-96 comprising *N*-[4-({4-(1-cyclohexen-1-yl)[(3,5-dichloroanilino)carbonyl]anilino}methyl)benzoyl]-β-alanine as a solvate

101. A composition according to any of the claim 100 comprising *N*-[4-({4-(1-cyclohexen-1-yl)[(3,5-dichloroanilino)carbonyl]anilino}methyl)benzoyl]-β-alanine as a solvate with acetone, butanol, ethanol 2-propanol or 1-propanol.

102. A pharmaceutical composition comprising, as an active ingredient a compound according to any of the claims 1-101 together with pharmaceutically acceptable carriers and/or diluents.

103. A pharmaceutical composition according claim 102 in a unit dosage form comprising from about 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg compound.

104. The use of a composition according to any of the claims 1-101 for the preparation of a medicament useful in the treatment and/or prevention of conditions mediated by glucagon receptors.

105. The invention provides the use of a composition according to claim 104 for the preparation of a medicament useful in the treatment and/or prevention of diabetes and/or obesity.

106. A method for the treatment and/or prevention of conditions mediated by glucagon receptors which method comprises administering to a subject in need thereof an effective amount of a composition according to claims 1-101.

107. A method for the treatment and/or prevention of diabetes and/or obesity which method comprises administering to a subject in need thereof an effective amount of a composition according to claim 1-101.

108. Use of a composition according to any of the claims 1-101, for the preparation of a medicament.

109. A process for the preparation a solvate of 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid comprising the steps of :

a) dissolving the parent compound as a free acid, an ester derivative or as a solvate of the parent compound, in same solvent as the solvate to be obtained or a different solvent or in a mixture of solvents

b) optionally heating the mixture

c) cooling the solution

d) isolating the precipitate

e) optionally drying the obtained solvate.

110. The process of claim 109, wherein the temperature in the optional step b) is below 150 °C, optionally below 85°C.

106. A method for the treatment and/or prevention of conditions mediated by glucagon receptors which method comprises administering to a subject in need thereof an effective amount of a composition according to claims 1-101.

107. A method for the treatment and/or prevention of diabetes and/or obesity which method comprises administering to a subject in need thereof an effective amount of a composition according to claim 1-101.

108. Use of a composition according to any of the claims 1-101, for the preparation of a medicament.

109. A process for the preparation a solvate of 3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-2*R*-hydroxypropionic acid comprising the steps of :

a) dissolving the parent compound as a free acid, an ester derivative or as a solvate of the parent compound, in same solvent as the solvate to be obtained or a different solvent or in a mixture of solvents

b) optionally heating the mixture

c) cooling the solution

d) isolating the precipitate

e) optionally drying the obtained solvate.

110. The process of claim 109, wherein the temperature in the optional step b) is below 150 °C, optionally below 85°C.

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C275/42 C07C211/27 C07C211/07 C07C279/14 A61K31/17
A61K31/13 A61P3/10 A61P3/04 C07C229/26 C07C215/08
C07C31/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K A61P C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/40446 A (NOVO NORDISK AS) 23 May 2002 (2002-05-23) cited in the application page 24, line 21 - page 25, line 18 claim 1	1-110
X	WO 02/40445 A (NOVO NORDISK AS) 23 May 2002 (2002-05-23) cited in the application page 25, line 16 - page 26, line 13 claim 1	1-110
X	WO 02/40444 A (NOVO NORDISK AS ; AGOURON PHARMA (US)) 23 May 2002 (2002-05-23) cited in the application page 25, lines 7-34 claim 1	1-110

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
22 June 2004	30/06/2004

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INTERNATIONAL SEARCH REPORT

National Application No
T/DK2004/000013

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/00612 A (NOVO NORDISK AS) 3 January 2002 (2002-01-03) cited in the application page 34, line 25 - page 35, line 24 claim 1	1-110
P,X	WO 03/051357 A (NOVO NORDISK AS) 26 June 2003 (2003-06-26) cited in the application page 9, line 21 - page 10, line 15	1-110
P,X	WO 03/053938 A (NOVO NORDISK AS) 3 July 2003 (2003-07-03) cited in the application page 17, line 17 - page 18, line 13 claim 1	1-110
X	US 2002/187982 A1 (BEHRENS CARSTEN ET AL) 12 December 2002 (2002-12-12) paragraphs '0195! - '0199!	1-110
X	WO 98/22109 A (CHANG LINDA L ; MERCK & CO INC (US)) 28 May 1998 (1998-05-28) page 15, line 30 - page 16, line 13	1-110
X	US 5 380 838 A (CVETOVICH RAYMOND ET AL) 10 January 1995 (1995-01-10) column 3, lines 20-31	1-110

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
T/DK2004/000013

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0240446 A	23-05-2002	AU 2350202 A	27-05-2002
		WO 0240446 A1	23-05-2002
		EP 1345891 A1	24-09-2003
		JP 2004513936 T	13-05-2004
		US 2003027849 A1	06-02-2003
WO 0240445 A	23-05-2002	AU 2350002 A	27-05-2002
		WO 0240445 A1	23-05-2002
		EP 1345890 A1	24-09-2003
		JP 2004513935 T	13-05-2004
		US 2003203946 A1	30-10-2003
		US 2002187982 A1	12-12-2002
WO 0240444 A	23-05-2002	AU 2350102 A	27-05-2002
		WO 0240444 A1	23-05-2002
		US 2003065031 A1	03-04-2003
WO 0200612 A	03-01-2002	AU 6583401 A	08-01-2002
		BR 0111908 A	01-04-2003
		CA 2411552 A1	03-01-2002
		CN 1437581 T	20-08-2003
		CZ 20024105 A3	14-05-2003
		WO 0200612 A1	03-01-2002
		EP 1296942 A1	02-04-2003
		HU 0301501 A2	28-08-2003
		JP 2004501897 T	22-01-2004
		NO 20026149 A	21-02-2003
		US 2004024045 A1	05-02-2004
		US 2002143186 A1	03-10-2002
WO 03051357 A	26-06-2003	WO 03047626 A1	12-06-2003
		WO 03051357 A1	26-06-2003
		US 2003138416 A1	24-07-2003
		US 2003229128 A1	11-12-2003
WO 03053938 A	03-07-2003	WO 03047626 A1	12-06-2003
		WO 03053938 A1	03-07-2003
		US 2003138416 A1	24-07-2003
		US 2003212119 A1	13-11-2003
US 2002187982 A1	12-12-2002	US 2003203946 A1	30-10-2003
		AU 2350002 A	27-05-2002
		WO 0240445 A1	23-05-2002
		EP 1345890 A1	24-09-2003
		JP 2004513935 T	13-05-2004
WO 9822109 A	28-05-1998	AU 730295 B2	01-03-2001
		AU 5442898 A	10-06-1998
		CA 2271893 A1	28-05-1998
		EP 0959886 A1	01-12-1999
		JP 2000514088 T	24-10-2000
		WO 9822109 A1	28-05-1998
		US 5880139 A	09-03-1999
US 5380838 A	10-01-1995	AT 179985 T	15-05-1999
		AU 681916 B2	11-09-1997
		AU 8013094 A	04-05-1995
		CA 2171871 A1	20-04-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No
T/DK2004/000013

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5380838 A		DE 69418469 D1	17-06-1999
		DE 69418469 T2	16-12-1999
		EP 0722454 A1	24-07-1996
		ES 2131219 T3	16-07-1999
		JP 2938974 B2	25-08-1999
		JP 9503521 T	08-04-1997
		WO 9510525 A1	20-04-1995
		ZA 9407863 A	22-05-1995